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GASTRIC SURGERY*

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SINCE this paper is presented before and will be read largely by physicians interested in the general practice of medicine, in it I will try to cover briefly many of the conditions in which surgery is applicable in the stomach, duodenum and jejunum, and our experiences with them. The latter two structures will be included because their surgical management, either by subtotal gastrectomy or by gastroenterostomy, involves the stomach at the time of the primary surgical procedure and even more seriously involves it when secondary complications, such as gastrojejunal ulcer and gastrojejunocolic fistulas, occur.

HIATUS HERNIA

If we consider gastric lesions in relation to their anatomic level, and start with the cardia, we can first consider the question of hiatus hernia and, together with hiatus hernia, peptic ulcer of the lower end of the esophagus, which occasionally develops as a result of the hernia.

Hiatus hernia is by no means an uncommon lesion. It is characterized by digestive disturbances and by pain beneath the sternum easily confused with anginal pain. It varies in intensity from acute episodes when good-sized sections of the upper stomach are trapped and distended in the hiatus hernia to the very vague digestive symptoms and very moderate degrees of distress that are associated with small openings through which but small sections of the stomach protrude into the pleural cavity (Figs. 1 and 2).

The management of most of these lesions has been successfully accomplished by the Gastroenterological Department of the clinic by medical measures.

Since most of the symptoms associated with hiatus hernia are the result of distention of the herniated portion of the stomach, nonoperative measures are directed largely toward the attainment of more normal digestive function and the avoidance of gastric distention. With the establishment of a careful dietary regimen and the avoidance of laxatives, there have been few of these patients who have but moderate-sized hernias in whom it has not been possible, without surgical interference, to maintain reasonable digestive comfort and to overcome the substernal pain of which most of these patients complain.

We have in the past in a number of these cases attempted to obtain relief by phrenicotomy, but with increased experience in their nonoperative management, this procedure has been rarely necessary, and in the cases in which it has been done it has not added significantly to the benefits that can be obtained by medical management alone.

FIGURE 1. *Roentgenogram of a Small Hiatus Hernia Associated with a Congenitally Short Esophagus.*

In hiatus hernias with large defects in which good-sized portions of the stomach pass through the

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diaphragm, repair of this defect has occasionally been necessary. It presents no technical problems of great difficulty except to be certain that the aperture is adequately closed without producing obstruction.

Peptic Ulcer of the Esophagus

Dr. Donald T. Chamberlain[1] has reported from this clinic the occurrence of 7 peptic ulcers of the lower end of the esophagus. One of these was due to the occurrence of a peptic ulcer in aberrant gastric mucosa; the remainder were associated with and probably brought on by hiatus hernia.

These lesions are probably brought about by the congestion in the mucosa as the upper end of the stomach and lower end of the esophagus rub against the edge of the aperture in the diaphragm, together

Figure 2. *Roentgenogram of a Sizable Hiatus Hernia above the Level of the Diaphragm.*

It is quite well distended and in the state of distention that produces symptoms.

with the fact that in the trapped segment of stomach there occurs a high gastric acidity, thus providing favorable conditions — congestion associated with gastric contents having high acid values — for the production of a peptic ulcer. These are the conditions that, when brought about in experimental animals, make it possible to produce experimental peptic ulcer (Fig. 3).

In patients presenting typical ulcer symptoms with high acidity, hunger pain and food relief, and in the absence of any visible defect in the stomach or duodenum as shown by the roentgenogram, one must have in mind the possible presence of such a peptic ulcer in the esophagus.

Dr. Everett D. Kiefer, of the Gastroenterological Department of the clinic, has set up the criteria for the diagnosis of these lesions: there must be a high

Figure 3. *Roentgenogram of a Small Hiatus Hernia Associated with a Peptic Ulcer.*

The ulcer is shown by the fleck at the point of the arrow. Note the relation of this ulcer to the diaphragm, which can be seen as a shadow. This patient was relieved of all symptoms by ulcer treatment.

gastric acid value; typical ulcer symptoms must be relieved by food and alkali; the ulcer must be visualized by esophagoscopy; and the symptoms must disappear after nonoperative ulcer management. All these patients have been successfully managed without operation, and the subject is discussed merely as a reminder of the occurrence of this lesion in a patient with ulcer symptoms but with no ulcer demonstrable in the usual locations.

Carcinoma of the Cardia and Lower Esophagus

One of the lesions that has now become surgically approachable is carcinoma of the cardiac end of the stomach, so often spreading over onto the lower end of the esophagus, or vice versa.

The surgical management of these lesions by means of the transthoracic approach has been so

well established that everyone should be on the lookout to diagnose carcinomas of the upper end of the stomach or lower end of the esophagus earlier than they have been diagnosed in the past. Carcinomas of the lower end of the esophagus and upper end of the stomach, on the basis of autopsy figures from large hospitals, represent 5 per cent of all carcinomas found at autopsy. Over the years our attitude toward malignant lesions in this location has been so pessimistic that we have not concentrated sufficiently on their early diagnosis. With these lesions now so removable by means of radical surgery, the slightest feeling of discomfort in the lower esophagus, the most trivial degrees of obstruction and the most vague digestive symptoms must be thoroughly investigated with regard to the possibility of this lesion if we are to make full use of the surgical facilities now at hand in attempting to cure a greater number of these patients (Figs. 4, 5 and 6).

FIGURE 4. *Preoperative Roentgenogram of a Carcinoma of the Lower End of the Esophagus.*

This was resected transthoracically through the diaphragm, the stomach being pulled up into the chest and anastomosed to the esophagus to make up for the defect.

Mortality figures in these patients submitted to resections of the lower end of the esophagus and upper end of the stomach are shown in Table 1. It is to be noted that, with increasing experience in the hands of Dr. Ralph Adams and Dr. Herbert D. Adams, who, because of their interest in chest surgery, have operated on most of these patients, the mortality has progressively diminished until it is now within very reasonable figures.

Gastric Ulcer

The problem of gastric ulcer is one that has occupied the attention of gastroenterologists and surgeons over a great many years, largely owing to the relation between gastric ulcer and gastric cancer.

Over the past years we have taken the position that a great many gastric ulcers can be healed and will remain healed under medical management. We have demonstrated this to our satisfaction, and if one could be certain concerning his ability to determine safely which lesion is benign and which lesion is malignant, I should personally be willing to continue with this program. But now, at the end of several years' experience with this position, I believe that it should be changed to the position that all gastric ulcers, provided the patient is a reasonably good risk, should be submitted to operation. This seems a radical position to take, particularly in the light of some of our previous statements, and some of our previous experiences with these lesions, which have healed under nonoperative management, but I have personally come to this conclusion for the following reason. The results in the surgical treatment of gastric cancers are so de-

FIGURE 5. *Postoperative Roentgenogram after Transthoracic and Transdiaphragmatic Resection.*

Note the clips of the von Petz sewing machine where the stomach has been transected and the end turned in. The anastomosis of the now intrathoracic stomach to the lower end of the esophagus and the dilatation of the esophagus during peristalsis are shown.

pressing that there must be some radical change in our attempts to deal with them earlier if we hope to improve these results. It has now been demonstrated beyond reasonable doubt that even in the presence of gastric cancer, apparent healing of the ulcerating lesion can be brought about under good medical management. We have, in addition, in suspicious lesions found it difficult, and at times almost impossible, to make patients return a sufficient number of times for adequate check-up examinations to be certain that what appeared to be a benign lesion was not developing into a malignant

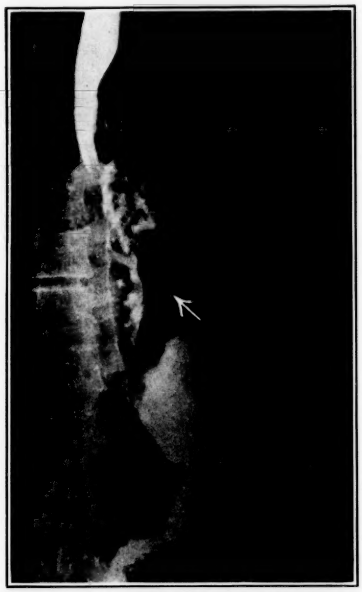

FIGURE 6. *Postoperative Roentgenogram after Transthoracic Resection.*

This illustration demonstrates how the duodenum has swung to the midline as the result of the altered position of the stomach and gradual traction on the duodenum.

Note again at the arrow the clips of the von Petz sewing machine, showing the transection of the stomach at its midportion.

one. We have now done high subtotal gastrectomies on 85 consecutive patients with gastric ulcer with no mortality. In view of the above consideration, we believe that if this be balanced against the constant danger of wrongly diagnosing a gastric ulcer for early gastric cancer, better results will be obtained and greater progress will be made in the management of gastric cancer by the position of advising subtotal gastrectomy in all cases of gastric ulcer. In a large experience with these lesions, some mistakes have been made in diagnosing ulcer when carcinoma was present, and this, together with a recognition of the fact that nothing but a more aggressive approach to gastric lesions in the way of early radical surgery will improve a field that is now far from satisfactory, brings me to this position.

As already stated, gastric carcinoma is almost the most depressing situation in the entire field of readily approachable surgical lesions. This is

TABLE 1. *Data on Resection of Cardia and Lower Esophagus.*

SERIES OF PATIENTS	NO. OF EXPLORATIONS	NO. OF RESECTIONS	NO. OF HOSPITAL SURVIVALS
First (7/1/37 through 12/31/43) ..	28	16	9
Second (1/1/44 through 4/26/46) .	29	14	13
Totals	57	30	22

primarily due to the fact that it is so rarely diagnosed early, which, in turn, is due to certain factors related to this lesion. It produces a low gastric acidity or an anacidity and so does not produce the digestive symptoms related to high acidity, as occurs with ulcer; it is an infiltrating lesion and so does not produce early hematemesis; the stomach is of such size that the growth of the lesion produces obstructive symptoms only in the late stages of the disease. As a result of all these factors, the lesion may be fairly well advanced before it produces symptoms of an urgent and distinctive character.

In addition to the above factors, the high vascularity of the stomach, the rich field of lymphatics that surround it and the fact that it is a structure in which active and vigorous motion exists with great frequency produce conditions for early extension outside of the structure itself and result in recurrence today, in spite of radical operation, in over 90 per cent of cases.

To improve the results in carcinoma of the stomach will be difficult. It will involve requirements and conditions that are almost impossible to attain, that is, more complete and involved investigations for relatively minor symptoms, such as earlier gastric analyses, gastroscopies, fluoroscopies and roentgenograms, more frequent explorations of doubtful lesions and the more universal establishment of the position that I am now willing to take, namely, that all patients with gastric ulcer should be submitted to radical surgery.

The mortality figures for the last consecutive series of cases of peptic ulcer are submitted in Table 2, involving cases operated on in the last ten years.

GASTRIC CARCINOMA

Two types of operation are available for the management of gastric cancer — high subtotal gastrectomy and total gastrectomy combined with

splenectomy in order to make the total gastrectomy more radical and the anastomosis of the jejunum to the esophagus easier and safer under good direct vision, as can be done with the spleen removed.

Because palliative operations, such as palliative gastroenterostomy, are so unsatisfactory, are done so often in advanced lesions, provide relief for such a relatively short period of time and have such a high

TABLE 2. *Mortality for Cases of Peptic Ulcer (October 1, 1936, to April 1, 1946).*

DIAGNOSIS	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Duodenal ulcer	358	10	2.8
Gastric ulcer	85	0	0.0
Jejunal ulcer	87	2	2.3

mortality rate, we have been less and less interested in doing them. This has resulted in employing subtotal gastrectomy in many of the advanced cases of carcinoma of the stomach in which in the years gone by a palliative procedure, such as gastroenterostomy, would have been performed. This has been done on the basis that an operation in which the lesion itself is removed even when a cure cannot be anticipated is superior to a palliative gastroenterostomy in which the lesion is left behind, soon to invade the new stoma.

This approach results, as might be expected, in a relatively high mortality, 12 per cent in 256 consecutive cases, as may be seen from the statistics (Table 3). It is, however, superior to the palliative operation, in which the mortality is almost twice this figure, 21 per cent.

There are a few things that we have learned in our experience with subtotal gastrectomy for malignant tumors. One is that the operation can be made

TABLE 3. *Mortality for Cases of Carcinoma of the Stomach (October 1, 1936, to April 1, 1946).*

OPERATION	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Subtotal gastrectomy	256	31	12.6
Exploration and biopsy	294	18	6.1
Palliative operation	66	14	21.1

more radical by combining omentumectomy with the subtotal gastrectomy, and the other is that to give these patients with malignancy a real chance, resection must be so high that it cannot be done with stomach clamps. For that reason, all subtotal gastrectomies performed at the clinic during the last eighteen years have been done with the von Petz sewing machine, making it possible to remove four fifths of the stomach in these cases, together with almost the entire omentum.

Omentumectomy, partial or complete, as shown in Figure 7, not only removes metastatically involved nodes in the omentum, so frequently present in cases of carcinoma of the stomach, but also exposes the posterior wall of the stomach, the gastric artery at its root and the posterior wall of the duodenum so satisfactorily and adequately that it not only increases the radicalness of the procedure but makes it technically much easier to do.

LEIOMYOMA OF STOMACH

In Figure 8 is shown the roentgenogram of a patient with leiomyoma of the stomach, and in Figure 9 is shown the specimen of such a case, removed by subtotal gastrectomy.

I wish particularly to call attention to this lesion, of which we have now had 14 cases. I am especially anxious to call attention to this group of cases because almost all these patients have a history of repeated hemorrhages. In the removed specimen (Fig. 9) will be seen the healed scars representing ulceration of the mucosa over this tumor.

Because of the fact that leiomyomas usually do not produce symptoms except for the frequently profuse hemorrhages that go with them, this bleeding is often suspected of being caused by ulcer and, unless adequate investigation is carried out, many of these patients are treated for ulcer because of the profuseness of the hemorrhage.

It is important that these cases be diagnosed early because of the fact, as I[3] have stated in a previous article on this subject, that 71 per cent of these tumors, on removal, have shown sarcomatous degeneration. It is for this reason that I particularly wish to call attention to them and their need for early and radical removal.

There has been no mortality in this group of cases.

TOTAL GASTRECTOMY

Our oldest living patient on whom total gastrectomy was done was operated on October 8, 1937, for a large leiomyosarcoma involving all the stomach. She is, therefore, now alive and well eight years and seven months after operation. This operation, of which we have now done eighty-nine, is really a development of the last ten years. We have applied total gastrectomy in the cases of leiomyosarcoma in which it has the most favorable prospect of cure in that these lesions may involve the entire stomach but still remain of a relatively low grade of malignancy.

We have applied this operation also to the lymphosarcomas because of the fact that, with partial gastrectomy, it is difficult in many of these cases to determine the limit of infiltration because these lesions do not produce a true tumor, but are infiltrating in character. The oldest patient of this group is alive and well seven years and one month after total gastrectomy.

We have also applied this operation to the infiltrating type of carcinoma of the stomach to which

the term "linitis plastica" has been given, owing to the fact that this type of cancer of the stomach, in contrad stinction to the localized type, tends to spend its energy more largely in intramural infiltration than in local extension and metastases to the lymph nodes. The oldest patient of this group is now alive and well without recurrence five years and four months after operation.

As already stated, it is in the first group, the multiple leiomyosarcomas involving the entire stomach, that there is the greatest prospect of cure by total gastrectomy, and it is unlikely in the patients with carcinoma that there will be cases in which the lesions are so extensive that total gastrectomy is indicated in which permanent cures can be expected.

Although it is true that in the linitis plastica type of carcinoma of the stomach, obvious metastases to lymph nodes are often not apparent, it is in all probability equally true, in the cases in which the entire stomach is so involved that total gastrectomy is indicated, that there will be no cases in which some distant metastases have not already taken place and ultimate recurrence is inevitable.

Our position regarding the use of total gastrectomy, therefore, can be stated in the light of our experiences to date with 89 cases in which this operation has been done. Even in cases with complete involvement of the stomach by carcinoma of the linitis plastica type, life can be and has been prolonged from a few months to five years and four months. In the linitis plastica type of carcinoma of the stomach cures cannot be expected, but prolongation of life with comfortable living can be anticipated in many of the cases, if properly selected. In leiomyosarcomas there is a reasonable prospect of cure even when the lesions are extensive and total gastrectomies must be employed. Between the optimistic prospect concerning cure that one may have with patients who have leiomyosarcomas and the pessimistic ultimate prognosis in those in whom the linitis plastica type of carcinoma exists, rests lymphosarcoma of the stomach so far as the prospects of a satisfactory future life are concerned. This experience with total gastrectomy, as shown in our mortality figures, has permitted us to draw certain conclusions: that the operation has now be-

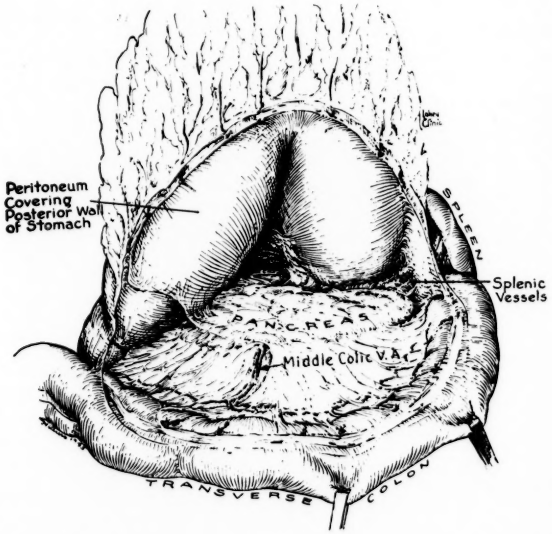

FIGURE 7.

This illustration shows how the omentum can be separated from the transverse colon for omentumectomy, together with subtotal or total gastrectomy, and also demonstrates exposure of the posterior wall, the gastric artery and the posterior wall of the duodenum (reproduced from Marshall[2] by permission of the publisher).

come sufficiently standardized in our hands and in the hands of many other surgeons so that it can be done with a reasonable mortality rate in spite of its magnitude; that patients can survive and live happily and maintain their weight and strength with no stomach and with the proximal loop of jejunum anastomosed to the esophagus, serving as a substitute for a stomach; and that it is necessary postoperatively throughout the remainder of their lives to keep close track of the blood picture in these patients, because of the tendency for anemias to occur. In almost all these cases it has been necessary for the patients to take liver, iron and vitamins. After operation, frequent meals must be

FIGURE 8. *Roentgenogram of a Leiomyoma of the Stomach. This shows the typical roentgenographic defect seen with these lesions.*

eaten — at least five a day — until at least a year or more has passed, by which time, in most of the cases, three meals of sufficient size can be taken at the regular intervals that have been established for all of us, and the interval feedings will not be necessary (Figs. 10 and 11).

Among the 89 cases of total gastrectomy there were 26 deaths, a mortality of 29.2 per cent, but of the patients operated on from January 1, 1942, through October 1, 1945, only 7 died, a mortality of 16.3 per cent.* The estimated chances of survival, based on 57 patients who survived operation and were followed, whether now living or dead, are as follows: 59.7 per cent have a chance of living for 12 months; 38.6 per cent for 18 months; 29.8 per cent for 24 months; and 21.1 per cent for 36 months or more.

*From follow-up data compiled by Dr. Frances H. Smith, Department of Gastroenterology, Lahey Clinic (to be published).

DUODENAL ULCER

Duodenal ulcer is the most complicated lesion in my opinion in the entire field of gastric surgery. In this clinic over the past years we have had passed through the Gastroenterological Department for management 8000 patients with duodenal ulcer, of whom approximately 6 per cent have come to surgery. The mortality rate was 1.5 per cent, but as a result of the occurrence of 4 fatalities in the last year is now 2.8 per cent for the past ten years.

This lesion, exclusive of gastrojejunocolic fistula, has associated with it the highest mortality rate in the entire surgical management of peptic ulcer. It will be noted in the statistical chart (Table 2) that in a consecutive series of 85 cases of resection for gastric ulcer there was no mortality, and that the mortality in 87 consecutive cases of resection for jejunal ulcer, which involves not only subtotal gastrectomy but also resection of the jejunum, was 2.3 per cent, even lower than that for subtotal gastrectomy for duodenal ulcer.

In discussing this lesion and its surgical management, I have again and again stated that the mortality of duodenal ulcer is not the result of the subtotal gastrectomy but of the relation of the duodenal ulcer to the head of the pancreas, into which it so frequently erodes, and to the common bile duct, to which it is so often intimately attached by the induration and scarring associated with it.

We have taken the position over the years that, when possible with reasonable safety, we should always remove the duodenal ulcer and that part of the duodenum in which it occurs. We do not believe that the removal of the duodenal ulcer is essential to bring about a cure with subtotal gastrectomy, but that its removal is often essential if one wishes to obtain enough flexible duodenal stump so that it can be safely inverted without the danger of a duodenal fistula. It has been our desire to avoid the occurrence of a duodenal fistula, representing as it does leakage, the danger of digestion of the fistula wall and the always possible occurrence of a fatality. It is for this reason, not the mere removal of the ulcer, that we have advocated that, included in the subtotal gastrectomy for duodenal ulcer, whenever reasonably possible, should be the removal of that portion of the duodenum in which the ulcer is situated, together with the ulcer.

Working, as we do, in very close and intimate relation to the members of the Gastroenterological Department of the clinic, it must be realized that practically all patients with duodenal ulcer coming to the Surgical Department for subtotal gastrectomy have ulcers of the chronic, recurring type, intractable to medical management and often asso-

ciated with complications, such as recurring hemorrhages or pyloric obstruction. This means that in a high percentage these patients on whom we do subtotal gastrectomy have badly scarred duodenal ulcers that have eroded into the head of the pancreas and into the pancreaticoduodenalis artery, which runs on the back wall of the duodenum, and as a result of the induration and scarring, often have pyloric obstruction.

Over the years we have adhered quite strictly without much change to what we have published in the past as our indications for surgery in duodenal ulcer. They are as follows: failure to relieve distress and pain by medical management; the occurrence of hemorrhage, particularly repeated hemorrhages, in spite of medical management; perforation, obviously an emergency indication for operation; and pyloric obstruction. This set of indications is so straightforward that they require little further discussion, except perhaps the matter of pyloric obstruction and hemorrhage.

I have repeatedly said that in the past we have often wasted time and money of patients with recurring pyloric obstruction by getting them into the hospital and in bed, where they have been relieved of emotional stress and strain, and by putting them on rigid dietary regimens and antispasmodics, with the result that in many cases the obstructions have been relieved, only to recur when the patients have resumed their work and activities under the stress and strain that frequently go with them, or when they have perhaps not adhered as rigidly to their dietary regimen as they should.

We have been disturbed at times by having to carry out surgical procedures on these patients late, at which time we have often thought that we should have done the operations sooner. We have sought, therefore, a plan whereby we could make earlier decisions in the patients with pyloric obstruction, particularly those related to duodenal ulcer, concerning when we could expect that the pylorus that we are able to open would remain open, when it would not remain open and when surgery was indicated.

Dr. S. Allen Wilkinson,[4] in the Gastroenterological Department, has developed and published a plan that has been of great help to us in making this decision. It consists of putting an indwelling Levine tube in the patient's stomach through the nose,

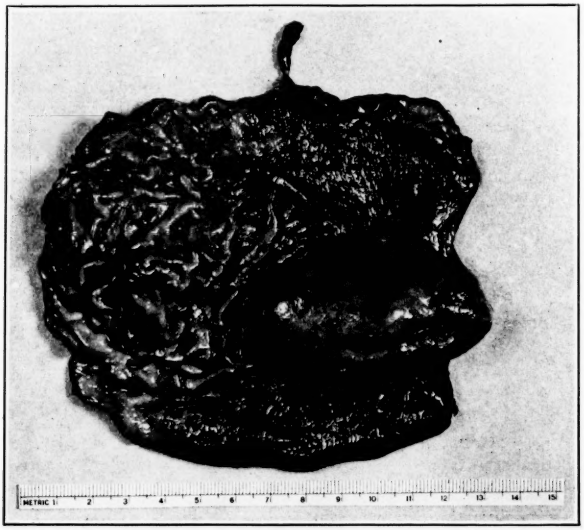

FIGURE 9. *Gross Specimen of the Leiomyosarcoma.*
Note the scars of previous ulceration and hemorrhages, as mentioned in the text. Microscopically this proved to be a leiomyosarcoma.

feeding the patient who is known to have pyloric obstruction a 90-cc. noncurding mixture through

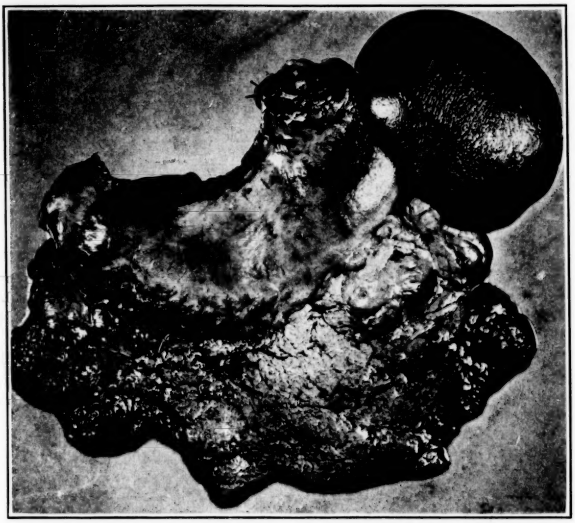

FIGURE 10. *Surgical Specimen of a Total Gastrectomy for Carcinoma of the Linitis Plastica Type.*

Note the entire removal of the stomach, the small cuff of duodenum with all of the omentum attached and the spleen.

the tube every hour for twenty-four hours and continuing this for three days. The tube is clamped for the first half-hour of each hour and is drained for the second half-hour, and the total amount of drainage obtained is recorded at the end of twenty-four hours. When, as shown in Table 4, which lists a few examples of such cases, the drainage does not decrease promptly within the three-day period from a high to a low figure, one can anticipate that the pylorus will not remain open and surgery will be necessary.

It is to be noted also in these patients who have pyloric obstruction that there is a time relation to the probability whether the pylorus will remain open under medical management. Table 5 shows that in those patients who had pyloric obstruction

TABLE 4. *Results of Tube Drainage in Nonoperated Cases of Duodenal Obstruction.*

CASE NO.	DURATION OF OBSTRUCTION	6-HR. RESIDUE	TUBE DRAINAGE*	RECURRENCE
		%	oz./day	
1	6 mo.	90	41-24-18	1 yr. (operation)
2	2 mo.	Large	34-33-7-2	None
3	?	25	22-27-35-1-0	None
4	3 wk.	90	50-42-24	1 yr. (operation refused)
5	3 mo.	Large	31-34-40	6 mo. (operation)
6	?	Trac	53-19-18-10	None
7	10 days	Trac	23-22-30-9	Hemorrhage (2 mo.); operation
8	4 mo.	50	45-20-4	None
9	10 mo.	Trace	26-22-6	None
10	2 wk.	10	21-20-9-3	None
11	2 yr.	90	44-45-50-41	3 mo. (operation)
12	2 mo.	70	24-5-1	None
13	2 yr.	Not known	56-23-31-17-19	Operation refused
14	5 mo.	90	20-5-1	6 mo. (operation)
15	?	50	10-10-10-4	None

*The figures represent the amounts on consecutive days.

for less than three months, 39 per cent[4] required ultimate surgery, whereas of those who had pyloric obstruction three months or more, an increased percentage (69 per cent) ultimately required operation. This has proved a valuable procedure in our hands in saving patients time in the hospital and permitting us to arrive at an early decision in patients with pyloric obstruction concerning when operation was necessary.

One should not leave the matter of bleeding without again calling attention to the fact that there are two types of bleeding associated with duodenal ulcer. The more frequent one, that with which everyone is quite familiar, is the case with an occasional single hemorrhage from which, in spite of a considerable loss of blood, the patient promptly recovers. Many patients with peptic ulcer become callused to hemorrhages of this type and do not look on them with undue apprehension.

In this type of bleeding there is no surgical emergency and the decision can be made deliberately concerning whether radical operation is advisable. It is our opinion, as stated above, that when such a hemorrhage occurs in spite of a good regimen of medical management, subtotal gastrectomy is indicated.

It is to be remembered, however, that there is another rare but extremely dangerous type of hemorrhage associated with duodenal ulcer — that is, the massive hemorrhage in which the bleeding persists and is of such magnitude and frequency as to result not infrequently in a fatality unless something desperate is done.

TABLE 5. *Results of Drainage in 100 Cases of Duodenal Obstruction.**

DURATION OF OBSTRUCTION	OBSTRUCTION RELIEVED	OBSTRUCTION RECURRED
	%	%
Less than 3 mo.	61	39
More than 3 mo.	31	69

*Of these patients, 56 were relieved by drainage and 44 were eventually operated on.

FIGURE 11. *Roentgenogram Taken Several Months after a Total Gastrectomy.*

Note the dilatation of the jejunum to serve as a substitute for the stomach. Note also the two loops of jejunum with an entero-enterostomy at the lowest point of the jejunal loop. There is no dilatation of the esophagus.

It is in these cases that an immediate decision must be made if these patients are to be saved. This decision must be made within forty-eight hours and often within twenty-four hours if, in spite of massive transfusions, one hopes to save these patients. It is to be remembered that hemorrhage is often more serious and fatal in patients over fifty years of age than in those under fifty years of age. This is not an easy decision to make, but in the presence of persisting and repeated hemorrhages from duodenal ulcers, where facilities and adequate experience are available, these patients should not be permitted to go on to such desperate states that ultimate surgery, when done, has little or no prospect of resulting in anything but a fatality.

Decision regarding what the approach to this serious problem is must remain in the judgment of the surgeon, based largely on what the patient will stand. In some of these cases we have saved the patient's life by subtotal gastrectomy, together with removal of the indurated ulcer, and control of the bleeding, even when the risk has been desperate. In others, so desperate has been the situation that we have opened the duodenum, transfixed the bleeding ulcer with silk and done a gastroenterostomy to overcome the obstruction that has resulted. The mortality in these cases will be high. In this selected group with recurring massive hemorrhages it is the only procedure, however heroic the measure may appear to be, that offers these patients a prospect of life.

As a result of this experience with subtotal gastrectomies for intractable duodenal ulcer, we can draw the following conclusions. The resection must be high (Figs. 12 and 13) in order to get out the largest number of acid-bearing glands. Our resections

have taken out as a minimum three fourths and in most cases four fifths of the stomach, and when it is reasonably possible, it is desirable to remove the ulcer and that portion of the duodenum in which it is situated. An antecolic anastomosis without enteroenterostomy has in our hands been the most satisfactory method of restoring the intestinal stream; it is not desirable to do an enteroenterostomy between the afferent and efferent loops of jejunum because of the fact that it sidetracks alkaline duodenal and jejunal contents beyond the stomach and prevents them from entering the stomach, as they do when no enteroenterostomy is done, thus helping to lower gastric acidity. When, as a result of subtotal gastrectomy, anacidity or acid values of 10 or below can be produced, there will be few if any gastrojejunal ulcers, and the end results will be good. It is not necessary in our experience after subtotal gastrectomy to do jejunostomies or to introduce indwelling Levine tubes into the stomach, since these patients can be fed almost immediately after operation and, if adequate stomas are left, drain quite promptly and are not, in the majority of cases, bothered by postoperative vomiting.

It is well to state to these patients that following subtotal gastrectomy they cannot eat anything they desire and cannot drink and smoke. If they wish to have the best prospect of nonrecurrence of their ulcers, in the form of gastrojejunal ulcers, they must remain on a postoperative diet that is almost as rigid as is the diet for the medical management of an ulcer that is to be treated without surgery. It must, I believe, be accepted that if a patient has once had an ulcer he is a prospect for another ulcer in spite of the high subtotal gastrectomy unless he takes every precaution in the way of change in his eating and living habits to prevent its recurrence.

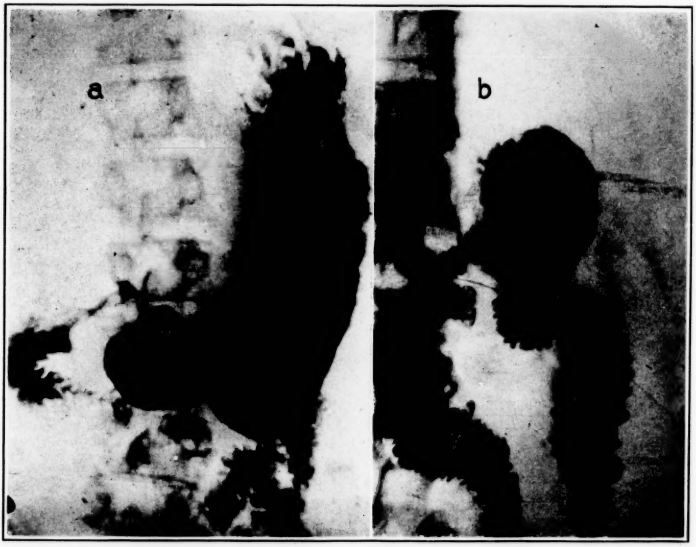

FIGURE 12. *Roentgenograms in a Case of Duodenal Ulcer.*

The one on the left was taken preoperatively. That on the right was taken after a high subtotal gastrectomy. Note the Hofmeister type of anastomosis, the small fraction of stomach remaining and the absence of any enteroenterostomy. These anastomoses are all of the antecolic variety.

JEJUNAL ULCER

Jejunal ulcer, sometimes called gastrojejunal ulcer, stoma ulcer or marginal ulcer, probably occurs in a much higher percentage of patients on whom gastroenterostomies for duodenal ulcer have been done than has been assumed to be true in the years gone by. What the exact incidence is, we cannot be absolutely sure, but it can safely be said to be over 15 per cent. In addition, as shown in our figures concerning the time gastrojejunal ulcer has

occurred after gastrectomy, it is not safe to assume that if a patient who has had a gastroenterostomy for duodenal ulcer goes three or four years, he is safe from the occurrence of this lesion. In patients coming here for surgery who have had gastroenterostomies for duodenal ulcers gastrojejunal ulcers have occurred as late as twenty-seven years after operation.

FIGURE 13. *Roentgenogram of a Patient Who Developed a Gastrojejunal Ulcer after a Subtotal Gastrectomy.*

The first operation, done elsewhere, was inadequate, and a second subtotal gastrectomy had to be done. Compare the extent of this resection with the resection in Figure 12 to demonstrate the radicalness of the procedure employed.

Jejunal ulcer is known to be an intractable type of ulcer, and used to be thought to be so intractable that surgery should be employed in every case. We have now dealt with a sufficient number of these cases so that we know that some of them can be handled medically and that, under such management, the ulcers will heal. In fact, it is our opinion that some jejunal ulcers occasionally heal spontaneously without accurate medical management. It is in all probability true that when a good gastroenterostomy has been done that later closes, the closure is the result of the cicatrix that follows the spontaneous healing of a gastrojejunal ulcer. We have several times seen such scars about the marginal stoma that brought about closure and must have been due to a healing of a previously existing gastrojejunal ulcer.

We believe that there is but one indication for immediate surgery in gastrojejunal ulcer, and that is when, as shown in Figure 14, it can be demonstrated that the jejunal ulcer is adherent to the transverse colon and in the process of perforating into the colon to form a gastrojejunocolic fistula.

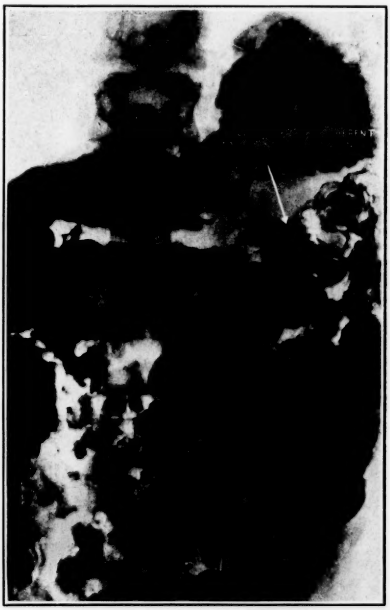

FIGURE 14. *Roentgenogram Showing a Jejunal Ulcer Adherent to the Transverse Colon.*

This ulcer was ready to produce a gastrojejunocolic fistula but, as proved by operation, it had not perforated.

In 87 consecutive patients who were operated on for gastrojejunal ulcer, the operation consisting of a high subtotal gastrectomy together with resection of that portion of the jejunum in which the stoma and the stomal ulcer existed, the mortality rate was but 2.3 per cent, demonstrating again that this lesion, although one of a complicated character, has even a lower mortality rate than that of duodenal

ulcer, again because of the fact that subtotal gastrectomy in duodenal ulcer, as already stated, is so often complicated by the fact that the ulcer is adherent to the head of the pancreas and to the common bile duct.

Gastrojejunocolic Fistula

Gastrojejunocolic fistula is by all means the most serious lesion with which one deals in gastric surgery. It is a perforation into the transverse colon of a jejunal ulcer that has become adherent to the transverse colon, producing a fistulous tract varying in size from one that will barely admit a straw to an aperture, as shown in Figure 15, the size of a ten-cent piece.

When large gastrojejunocolic fistulas occur, they result in a most undesirable physiologic state. They produce a condition that is comparable with pellagra and a weight loss that is often startling. This is due to the fact that the constant escape of feces into the stomach discourages the desire for food and the constant escape of gastric contents into the transverse colon results in a pellagra-like state because it does not permit a good fraction of the food ingested to pass through the small intestine, where it can be absorbed for proper nourishment.

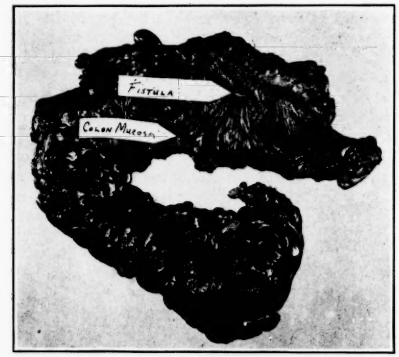

Figure 15. *Specimen Removed at the Second-Stage Operation for Gastrojejunocolic Fistula.*

The operation consists of partial colectomy, partial removal of the jejunum and subtotal gastrectomy. The gastrojejunocolic fistula is indicated by the arrow. Note its size and the amount of food that can be lost through it into the transverse colon.

We have been through the employment of all types of procedures in an endeavor to handle patients with gastrojejunocolic fistulas successfully, and it was not until I devised the plan of cutting off the ileum at the ileocecal valve, turning the distal end in, and anastomosing the proximal end to the descending colon beyond the gastroenterostomy and the fistula, with later subtotal gastrectomy and removal of the involved colon and jejunum, that we began to manage these cases successfully (Fig. 16).

I devised this plan of procedure with the idea that I could so advance that portion of the fecal stream in the small intestine beyond the gastroenterostomy that less of the colonic contents would pass back into the stomach; that it would establish the fecal stream beyond the gastroenterostomy so that at the second stage of the operation when the subtotal gastrectomy together with the removal of the involved colon was undertaken, the anastomosis between the descending colon and the terminal ileum would already have been established and functioning. This operation has been successfully applied in 20 cases. In 2 of these the anastomosis of the ileum to the descending colon, a procedure that diverts the fecal stream from the ascending and transverse colon, has resulted in spontaneous closure of the fistulous tract after the first stage of the

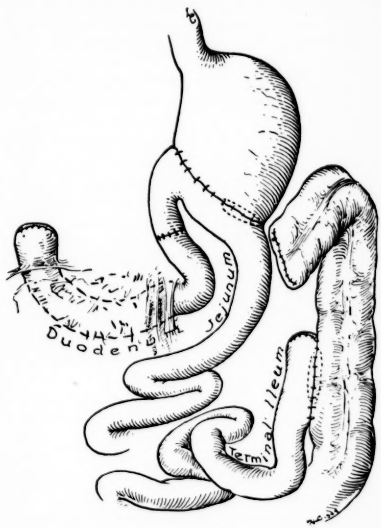

Figure 16.

This illustration shows the completed procedure for handling subtotal gastrojejunocolic fistula. Note the anastomosis of the ileum to the descending colon, which is the first stage of the operation. At the end of three months these patients return, at which time the ascending colon, transverse colon and the section of the jejunum in which the ulcer and fistula exist are removed in one piece, and a subtotal gastrectomy is performed. This illustration shows the status of the gastrointestinal tract when both stages of the operation are completed (reproduced from Marshall[8] by permission of the publisher).

operation and has resulted in there being no necessity for doing the radical second stage of the procedure to remove the fistula and the jejunal ulcer, together with the transverse colon.

It has been our experience in the remaining 18 cases in which the second stage of the operation has been done (Fig. 16), that if these patients are sent home for two to three months following the anastomosis of the ileum to the descending colon, thus advancing the fecal stream beyond the fistula, they will return at the end of this time in much improved general condition, with a gain in weight and with such improvement that the radical procedure of the second stage can be employed with a reasonable prospect of survival.

When one at first views this procedure, it appears to be so extensive as to unduly impress one with its magnitude. As we have done more and more of these operations, we have become aware that, with the fecal stream already established beyond the fistulous tract and with the patient in improved condition, it is possible, with reasonable ease, to cut the transverse colon off between the two rows of clips put in by the von Petz sewing machine beyond the fistula, just proximal to the splenic flexure, to turn the two ends in safety and to mobilize and devascularize the ascending colon and transverse colon, at which time the exposure becomes so adequate and complete that the operation, which consists of removing four fifths of the stomach, the involved segment of the jejunum and the ascending and transverse colon with the fistula into the splenic flexure, can be done more easily than the operation of subtotal gastrectomy and the removal of the jejunum alone in jejunal ulcer.

This is an operative plan for this serious lesion that offers the following advantages: the prospect that in a small percentage of cases following the implantation of the ileum into the descending colon, the fistula will heal spontaneously and the second stage of the operation will be unnecessary; and the fact that the marginal ulcer, together with the fistulous tract into the colon and that portion of the stomach to be removed in the subtotal gastrectomy, can be removed in one block without spilling colonic contents and without the dangers of colon-bacillus contamination that go with any operative procedure in which a fistula into the colon has to be opened and the fistulous tract into the colon closed.

This procedure in our hands has made it possible to deal with these patients with gastrojejunocolic fistula, who are so often emaciated and in extremely poor condition, more satisfactorily than with any other type of procedure that has been proposed.

In the last ten years, this operation has been performed in 22 cases, with 2 deaths, a mortality of 9 per cent.

* * *

I have purposely avoided any detailed discussion of technical surgical procedures in this oration before this general audience.

The mortality rates in the four types of peptic ulcer — gastric, duodenal, jejunal and gastrojejunocolic fistulas — are given, as well as those of radical operations and of palliative operations for malignant lesions of the stomach.

The type of lesions in which total gastrectomy has been applied in 89 cases and the total mortality in this group, together with the change between the mortality rate in the first 46 cases and that in the last 43 cases, are included.

Some of the measures by which the now unsatisfactory end results of surgery for gastric cancer can be improved are stated.

The mortality rate with transthoracic resection of the lower end of the esophagus and cardiac end of the stomach is reported again in two groups to indicate the improvement, as in total gastrectomy, that has come with added experience and improved selection.

Hiatus hernia, peptic ulcer of the esophagus and leiomyoma of the stomach are discussed, as are gastric ulcer, duodenal ulcer, jejunal ulcer and gastrojejunocolic fistula, and experiences and mortality rates in handling this group of cases are given.

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PRESIDENTIAL ADDRESS*

MOTIVATIONS AND OPPORTUNITIES

JAMES RAGLAN MILLER, M.D.†

HARTFORD, CONNECTICUT

THERE are two kinds of motivation that incite men to activity — those that push and those that pull. Hunger, thirst, cold, want and fear are motivations of the "pusher" type. These are sufficient on occasion to furnish a certain amount of activity, even in the most indolent. The classic example of this type of motivation is the burr strategically placed near the rear end of the donkey. By reputation the burr is an effective measure in these circumstances to activate this obstinate animal.

On occasion the same obstinate donkey can be led along the path of progress by a "puller" type of motivation. A bit of hay located at the front end makes use of his weakness for appetizing fodder. This type of motivation is subtler than the first. It will not work if the animal is already fed or if the quality of fodder is poor, and it seems sometimes that the pure cussedness of the beast resists all stimulation, whether from the front or from the rear.

Physicians prefer to think that they are motivated by altruistic considerations of the puller type. Analogies like ripe fruit are good only for a brief period of ripeness, and although I should not have you think that I believe that medical organizations act like donkeys, I recall the elder statesman who in commenting on an approbrious epithet that one of his colleagues had used in reference to another said, "I should not classify our colleague by that term, but since it has been used I understand perfectly what is meant." It will do us no harm occasionally to see ourselves as others see us, even though the exercise does not increase our self-complacency. The public has a high regard for the individual physician but is critical of us as a social group. To put it in the vernacular, they think that we have a "swell racket." This criticism has, in a measure, crystallized in a series of socialistic provisions for medical care by government that you all recognize as centered in the Wagner–Murray–Dingell Bill. It appears to me that this threatening legislation, much as we dislike it, has nevertheless served as an effective pusher type of motivation, operating on organized medicine to produce not only resistance to the unsound legislation itself but to strengthen liberal movements within medicine that promise much for the good of society.

Meetings of the New England Surgical Society are usually devoted to the discussion of clinical topics. Nevertheless, more than one president has seen fit to discuss some of the organizational problems that are encountered in the hospital, and it is my observation that the members have welcomed such a discussion. I too shall indulge in this exercise.

In his presidential address before this society in Hartford in 1932, Dr. Frank H. Lahey told us that if physicians do not take more interest in the management of the hospitals in which they work, they will gradually find themselves working not in but for those hospitals. This same advice holds good on the state and national level today. If physicians are to retain a dominant influence in the provision of medical care, they must raise their eyes more than occasionally from the sickbed or the operating table and help to solve the intricate problems of programming that are before us.

You are all familiar with the Hill–Burton Bill, which at present seems destined in some form to pass the present Congress. This bill calls for the study of the need for hospitals and health centers and provides for some construction where needed. It is important for us to remember that this bill as modified has the endorsement of the American Medical Association. When it goes into effect, we shall be compelled to think constructively in terms somewhat larger than has been our habit in the past, when our concern has been mostly with the management of our own individual hospitals. We shall have to plan for participation in a much more complex system of large and small hospitals, so integrated that skills and facilities can be made more generally available to the public.

In New England, as much as anywhere in the country, it has been a characteristic of the organization of medicine that it is decentralized and highly individualistic. I should be the last to wish to lose the advantages of this habit. We should, however, recognize some of its disadvantages and limitations. When physicians act as members of a group, they do so on three levels. The most significant group for the New England doctor is his hospital staff. Here the problems are almost exclusively clinical and have to do with the care of his patients. Next in order of significance in his mind is the local medical society or academy of medicine. He will attend its meetings if there is a good clinical program, otherwise not. Last of all comes his county or district association. This is the backbone of the guild organization, but here also clinical programs must be supplied to get a good attendance. Special regional

*Read at the annual meeting of the New England Surgical Society, Poston, February 6, 1946.

†Visiting obstetrician and gynecologist, Hartford Hospital.

and national societies also absorb the interest of many physicians, especially those who have the greatest capacity for leadership.

Just at this point it appears to me there is an opportunity for us to develop a program, as in fact we must do under the Hill–Burton Bill, by enlisting the interest of many whose talents for organization have hitherto been developed only within their own hospitals. I believe that it should be possible in some way to bring together those who are concerned with matters of staff organization in hospitals and to make them realize their dependence on the welfare of the whole guild of medicine. Policies of staff relations to boards of directors, to community physicians, to insurance carriers and to plans for medical care and kindred topics would be eagerly discussed.

It should be possible for each state medical society at its annual meeting to arrange for a conference of hospital staff officers. In such gatherings discussion should be limited to matters of an organizational nature. I am familiar, of course, with the work that the American College of Surgeons has done along this line for many years. Dr. Walter G. Phippen and many another member of the Society have been interested, as you know, but so far none of us have been able to capitalize for the benefit of organized medicine the tremendous resources of ability that develop in hospital staffs. State medical societies could do their members a great service if they would recognize how deep is the interest of many of their members in these problems and how great would be the support for a section on hospital staff affairs if developed exactly as other specialties have been organized. Here also would be a forum for the discussion of the problem of the ordinary practicing physician who has no staff connections. Here too could be discussed many problems that arise in connection with prepaid medical and hospital plans.

Such conferences as I have suggested would hasten the day when responsible staff members would sit at regular intervals throughout the year with the board of trustees of the hospital. Whether or not they have a vote is immaterial. Some hospitals have already established such intimate relations, although there are too many the staff and trustees of which view each other with a certain amount of suspicion.

The motto of such staff representatives might well be a paraphrase of the lines of Richard Lovelace: "Stone walls do not a prison make, nor marble halls a hospital." I do not have to labor this thought before the New England Surgical Society, but it is one that should be mentioned again and again in the councils of hospital management. Frankness, honesty, initiative, originality, clear thinking and seriousness of purpose are not items that appear prominently on the balance sheets of any organization, but they are ingredients failing which no institution can long survive, and those who budget for hospital care must make due provision for their cultivation.

I believe that the time is ripe for us to make a bold experiment in medical education, one that may never have been contemplated in just the terms that I wish to propose. I am thinking particularly of our situation in the New England states, although some western states have developed certain of its features. Except in teaching hospitals and in a very few of the nonteaching centers, we must admit that the intern does not get a good postgraduate education. At least it is not nearly so good as we know how to give. He feels that he is merely an extra pair of hands with legs and fountain pen attached. Most of the nonteaching internships would not be selected by a physician for his own son except perhaps in his own hospital, with the hope of thus assuring him a speedier and easier entrance into local medical practice.

In the report of the subcommittee on intern curriculum prepared for the Connecticut Postwar Planning Board's Committee on Medical Care and Health, the following statement was made:

> The studies initiated by the committee were for the purpose of determining how intern service in many Connecticut hospitals could be improved and made more attractive, to the end that the recruitment of house staffs for Connecticut hospitals might be more adequate in the future and thereby increase the usefulness of the hospitals and attract well trained physicians to the state for intern training, with the possibility that they might permanently locate in practice here to make up natural losses.

Among other things the committee recommended the employment of full-time or part-time medical personnel to cover the fields of pathology, radiology, anesthesiology and psychiatry for all hospitals of more than 100 beds. For those of more than 200 beds it was recommended also that a full-time physician be employed as a teacher to co-ordinate the hospital's educational program for interns, residents and staff members.

Such a program comes face to face with practical considerations of financing. Only a small part of it may be added to the patient's per diem charges, although he benefits from it directly as well as indirectly. If a satisfactory teaching program is developed, even though every expedient be employed to activate the voluntary services of the unsalaried staff, the costs will be more than can be borne without subsidy from private or public sources.

Medical schools that in the past have kept income and expense budgets on speaking terms with each other are greatly concerned with diminishing returns from private sources and are exploring the possibilities of government support. It is well known that the springs of private philanthropy are gradually drying up. Federal subsidies have not appealed to the New England mind because of the objectionable federal control that goes along with such subsidies, and if we are realists we should look at the huge national debt and become cautious when we think of federal subsidies in relation to long-range planning. In contrast to the federal treasury, how-

ever, the financial condition of most of the states is extremely secure, and the state treasury is the natural source of help that should be developed in the future.

Now that the G. I. Bill of Rights is lifting part of the financial burden, I believe that it might be possible to obtain subsidies from state legislatures for a teaching program in hospitals possessing some of the features that I have outlined.

In Connecticut there has been much talk of establishing a medical department of the University of Connecticut. I do not know how far this movement will go, but it is stimulating to talk about it. If it were possible to buy a medical school and install it as one would an air-conditioning system in one's home, it might be that the cost would run to something between $15,000,000 and $40,000,000, including endowment. The cost, as you well know, would depend a good deal on the extent of the program and on the number of "ivory towers" that are built in. This, of course, would be the undergraduate medical school of the customary type, and I think that most legislatures would not be responsive to a program of such magnitude.

Although many persons, including myself, believe that an undergraduate medical school should be developed by the State of Connecticut, the need of the day, as I see it, is not so much for undergraduate medical education as it is for continued instruction after the doctor comes out of medical school. Postgraduate instruction should become a permanent part of the system of medical education, and its development should take place whether or not there is an accompanying undergraduate curriculum. Each would complement the other. No vast building program is necessary for such a program, for we already have the buildings, which are our own hospitals. All that is needed is a faculty, a large part of which is to be found in the hospital staffs. I am merely suggesting that these facilities be brought together in a more formal manner, placing on the governing board adequate representation of hospitals, medical societies, the university and the legislature. Medical teaching should be at three levels, those concerning the intern, the resident and the staff — which of course includes the courtesy staff. The university would furnish the dean's office and the academic mechanisms for the program, and through it would come adequate compensation for those who carry on the burden of teaching. From the point of view of the intern and resident, the university could assure each one that he would get a training of high quality in his postgraduate years.

Tax-supported hospital systems have too often been veritable badlands of medicine. Exceptions to this rule are chiefly notable because they are exceptions. Now, badlands and deserts can be made to bloom by irrigation, and for the badlands of medicine the irrigation must be from the springs of medical education. This is the ray of hope that illuminates the future of the Veterans Administration under the plans of Generals Bradley and Hawley and our own General Cutler. Vast museums of living examples of various diseases in our state and municipal institutions are going to waste unused by our system of medical education. Is it not possible that this source of material can in some measure make up for the shrinkage of our ward services that has taken place under the influence of prepaid medical and hospital plans?

* * *

In these few remarks I have made two suggestions that have admittedly been very incompletely developed. Each may stand alone, although together they are complementary.

First, organized groups of hospital staff officers might be developed into sections in the state medical societies. Second, postgraduate medical education is needed on three levels, those of the intern, the resident physician and the community physician. This could be developed at moderate expense by a combined effort of the medical societies, hospitals, a state university and the state legislature.

If imagination is needed to recognize the opportunity that lies before us, aggressive and courageous leadership will be necessary to develop it. Great generosity and largeness of spirit will be necessary to adjust many local and personal obstacles, but these are not times when medicine can afford to let the ambitions and prejudices of little men obstruct the proper development of all our resources to give full medical service to the public.

179 Allyn Street

ACUTE HEMOLYTIC ANEMIA IN PRIMARY ATYPICAL PNEUMONIA ASSOCIATED WITH HIGH TITER OF COLD AGGLUTININS*

Report of a Case

MAJOR HAROLD S. GINSBERG, M.C., A.U.S.

SEVERAL observers[1-4] have reported cases of acute anemia occurring in patients with primary atypical pneumonia who have developed high titers of cold agglutinins (autohemagglutinins). Since all these patients, with 2 possible exceptions, had been given one of the sulfonamide drugs, an additional etiologic factor was present that these authors thought might have been the primary or a contributory cause of the hemolytic crisis.† In the case reported below, no sulfonamide drug or any other medicinal agent was used that could have been an etiologic factor responsible for the causation of the acute hemolytic anemia.

CASE REPORT

The patient, a 34-year-old soldier, was admitted to a United States Army general hospital on February 2, 1944 with a 24-hour history of increasing malaise, frontal headache, sore throat, cough slightly productive of yellow sputum, fever and chilliness, slight shortness of breath on moving about or talking and generalized muscle aches and pains. The past history was negative except for an episode of nasopharyngitis 3 weeks before the present admission.

On physical examination the patient was slightly uncomfortable and was coughing frequently. The cough was productive only of small amounts of frothy white-yellow sputum. There was slight tachypnea but no orthopnea and no dyspnea except with effort, and no cyanosis. The temperature was 102°F., the pulse 86, the respirations 19, and the blood pressure 122/82. The skin was extremely hot, dry and elastic; the color was good. Examination of the lungs revealed no abnormalities. The remainder of the physical examination was negative. The hemoglobin was 85 per cent (Tallqvist) and the white-cell count 9250, with 75 per cent neutrophils, 22 per cent of which were stab forms. Urinalysis and a blood Kahn test were negative.

The morning after admission the temperature was 103°F. (Fig. 1), the respiratory distress on effort had increased somewhat, and the cough had become slightly more productive. Scattered, fine, moist, crepitant rales could be heard over the left upper lobe anteriorly. A portable roentgenogram of the chest revealed a patchy density of the left upper lobe and the upper portion of the left lower lobe. The sputum smear and culture revealed no pathogens, and blood culture showed no growth. There soon developed slight dullness over the entire left lung, and numerous rales were heard throughout it. The white-cell count began to climb slowly, but owing to the fact that the sputum never assumed the characteristics of a bacterial pneumonia by gross examination, direct smear or culture, sulfonamide therapy was not begun. The titer of cold agglutinins in the peripheral blood on February 5 was ++++ in a dilution of 1:4.

Beginning on February 7, the patient began to feel much better, and the temperature appeared to be beginning a slow decline. The dyspnea and cough remained as prominent symptoms, and examination of the lungs showed no change. On February 9, the temperature for the first time fell to normal throughout the morning, and the patient felt greatly improved. By the following morning, however, a new chapter proved to be commencing. At that time the patient stated that he felt much weaker. Dyspnea still appeared rather prominent, and he was slightly cyanotic, but the pulmonary signs were unchanged. That afternoon slight icterus was first noted; otherwise physical examination revealed no change. The liver was not palpable, and the patient seemed to be in no distress. On the following morning the hemoglobin was 60 per cent (Tallqvist) and the white-cell count was 44,350, with 93 per cent neutrophils, 37 per cent of which were immature forms. The urine was reddish-brown, negative to the benzidine test and positive for bile and urobilinogen and gave a ++ test for albumin. The sediment showed 1 or 2 white cells per high-power field.

Within a few hours the hemoglobin was 45 per cent (Tallqvist), the red-cell count 1,360,000, the hematocrit 19 per cent, and the white-cell count 40,850, with 99 per cent neutrophils, 36 per cent of which were immature forms. Thus, the Wright-stain preparation of the blood smear revealed a typical leukemoid picture. Two nucleated red cells per 100 white cells were seen, and spherocytosis and polychromatophilia were noted. The red-cell count could be done only by first warming the diluting fluid. The direct platelet count was 451,520. The bleeding time was 6 minutes, and the clotting time 10 minutes; the clot retractility was good. The icteric index was 52. Urine urobilinogen was present in a titer of over 1:1000. There was bile in the urine but no blood. Bile was also present in the stools. Hemoglobinemia was present. Gross agglutination of the blood at room temperature was observed, even in high dilutions; this disappeared by warming above 37.5°C. Blood for determination of the titer of cold agglutinins was drawn, but could not be done for several days owing to lack of an adequate icebox. The Donath–Landsteiner phenomenon was negative. No sickling was observed in a sickle-cell preparation. No acid hemolysin was present in the serum. Blood allowed to clot and retract slowly at room temperature hemolyzed slightly.

Between the first laboratory tests and the completion of the second set of determinations the condition of the patient changed rapidly from that of a moderately uncomfortable patient to that of one who was so seriously ill as to be practically moribund. The blood pressure gradually fell from 124/70 to 100/44.

The typing of the patient's cells was not possible at incubator temperature, as well as at room temperature, owing to the high degree of adsorption of the agglutinin by the red cells; similarly, cross matching could not be performed. It was decided to use the specific type of blood, Type B, as determined by the patient's Army identification tags, rather than to use an uncross-matched blood of a universal donor.

Following alkalinization the patient was given 500 cc. of blood, which was kept warm throughout the transfusion. The blood was given over a period of 40 minutes, and no reaction occurred. Early the next morning 1000 cc. of Type B blood was given, following which the patient appeared and felt much better. Blood taken for laboratory studies 1½ hours after the second transfusion revealed a marked improvement over the preceding day. An extremely slight increase in the fragility of the red cells to hypotonic saline solution was found. Agglutination of the blood at room temperature still occurred. The same afternoon the dyspnea seemed to be tiring the patient so much that oxygen by means of a mask was begun, from which the patient received considerable relief, both objectively and subjectively.

On February 14, rales were first heard over the right lower lobe and right middle lobe; they were fine, moist and crepitant and were scattered throughout these lobes. An x-ray film of the chest taken the following day showed coarse mottling throughout the right lung; the process on the left had cleared somewhat, but there were still fairly coarse, mottled densities in the upper third and lower half of this lung. The

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†Since this paper was prepared and submitted for approval by the office of the Surgeon General, Finland et al.,[5] in their series of papers on the laboratory and clinical features of cold isohemagglutinins, reported 11 cases of anemia of varying severity occurring in cases of primary atypical pneumonia having significant titers of cold agglutinins. In 4 of these, a marked drop of hemoglobin from 40 to 70 per cent occurring over a period of three days or less was noted; in 1 case no sulfonamide was given before the onset of the hemolytic anemia. Four of the patients in the entire group had received no sulfonamides before the development of the anemia.

blood picture continued to improve, so that on February 15 it was believed that a transfusion would not be necessary, and only intravenous fluid was given. On that day the hematocrit fell from 32 to 29 per cent and the red-cell count from 3,240,000 to 2,350,000. For this reason blood transfusions were again started the following day, 500 cc. being given daily for 3 successive days. For the next 2 days, February 19 and 20, the blood levels maintained themselves, but on February 21 the hematocrit fell from the 32 per cent of the previous day to 29 per cent, with a corresponding drop of the hemoglobin and red-cell count. There was no rise of the

The subsequent course was one of gradual improvement in both the clinical and laboratory findings. No further transfusions were required. The patient was given large doses or oral and parenteral vitamins, ferrous sulfate and a high-vitamin diet. The red cells gradually increased in number, and there was a concomitant decline in the titer of cold agglutinins in the serum. The pneumonic process resolved slowly, but by March 28 the lungs were entirely clear on both physical and roentgenographic examination. Despite the complete clearing of the lungs, the patient continued to have low-grade fever, with a temperature between 99 and 100°F.

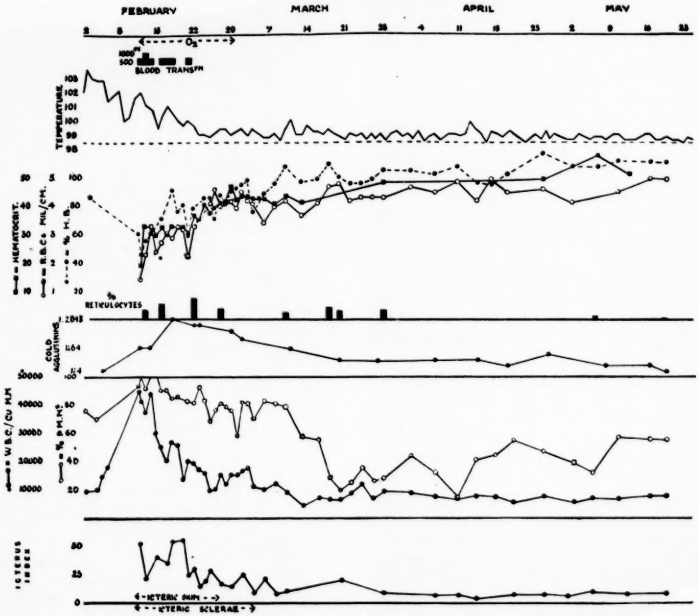

FIGURE 1. *Clinical Course and Essential Laboratory Findings.*

icteric index. Accompanying this fall in the levels of the red-cell components the patient stated that he felt weaker. He was sweating considerably, the pulse rose from 100 to 120, and dyspnea appeared prominent. The blood pressure was maintained. In the fear that another hemolytic crisis was imminent, 500 cc. of whole blood was again given, following which the pulse and respiratory rate diminished, and subjectively the patient was better.

At that time the titer of cold agglutinins in the serum was 1:2048, this probably being the first correct titer obtained.

On February 22 for the first time the lower border of the liver could be palpated as a rounded, nontender, firm edge 3.5 cm. below the right costal margin in the midclavicular line. The organ had been enlarged to percussion since February 17, and a definite sense of resistance in the right upper quadrant of the abdomen had been felt. The liver remained this size for 4 days and then began to recede gradually, so that on March 2 it could no longer be palpated. The spleen was not palpable throughout the course of the illness.

in the afternoon and evening. This continued on a diminishing level until he was essentially afebrile after April 21.

At discharge on May 29, the patient was asymptomatic and the laboratory findings were normal. The cold agglutinin titer was 1:4. The patient was returned to full duty.

This patient developed an acute hemolytic anemia with the presence of a high titer of cold agglutinins (autohemagglutinins), and the decrease of the anemia roughly followed a parallel course with the decrease of the cold agglutinins in the serum. None of the other factors that may cause such a hemolytic crisis were present. The Donath–Landsteiner phenomenon was absent, there was no acid-hemolysin, and no sickling tendency was present. There was a slightly increased fragility of the red cells to hypotonic saline solution.

Owing to lack of facilities, it was impossible to perform several laboratory tests that might have been illuminating both during the acute illness and during the convalescence. The lack of them does not, however, detract from the important features in this case.

It was impossible to do the usual hepatic-function tests, so that the true status of the liver function during the acute illness, as well as during convalescence, could not be determined. There is, however, no clinical reason to believe that there was any decreased function at the time of discharge. The plasma proteins, prothrombin time and icteric index at discharge were normal; the hippuric acid excretion was slightly diminished (2.83 gm., oral test).

The cold agglutinins react as do other agglutinins in that they can be adsorbed by red cells at 0 to 5° C. and in some cases even at room temperature, as was true in this case. The venous blood removed from February 12 and 14 was by an oversight allowed to separate slowly at room temperature, and without separation of the serum from the clot was placed in the icebox, which was at a temperature of about 10°C., until February 18, when the icebox was for the first time well enough regulated to maintain a temperature between 0 and 5°C., at which time these two serums as well as one drawn on February 18 were tested. The cold agglutinin titer of the later serum, which was separated immediately, the test being performed the same day, was 1:2048. Keeping in mind the fact that bloods drawn on February 12 and 14 showed autoagglutination at room temperature, we have every reason to believe that the actual titer in each serum was much higher than the test indicates.

Owing to the nonavailability of potassium dichromate at the time of the acute illness, it was impossible to make accurate standards for the determination of the icteric index. This accounts for the somewhat irregular curve of these determinations.

Discussion

The development of high titers of cold agglutinins (autohemagglutinins) was first reported in a large series of patients with primary atypical pneumonia of unknown etiology by Peterson, Ham and Finland.[1] This observation was confirmed by Horstmann and Tatlock[2] and shortly afterward by Turner, Nisnewitz, Jackson and Berney.[6]

Peterson et al.[1] first noted the presence of high titers of cold agglutinins in primary atypical pneumonia in 2 cases of the prevalent type that developed an acute hemolytic anemia during the course of the pneumonia. The presence of the reversible autohemagglutinin (cold agglutinin) was discovered when the difficulties of blood grouping and cross matching were met. Shortly afterward a similar case was seen by these writers. In 2 of the above cases sulfonamides had been used,[7] so that the causative agent of the hemolytic crises was of necessity in doubt. The third patient died before adequate laboratory data could be obtained.

Horstmann and Tatlock[2] likewise reported 2 cases of primary atypical pneumonia that had a titer of cold agglutinins and developed an acute hemolytic anemia. In 1 of these cases, which was fatal, they reported that the patient had had sulfadiazine nine days before the development of anemia, and stated that the part that the drug played in the anemia was unknown. It was not mentioned whether the second patient, who recovered, had received a sulfonamide drug.

Dameshek[3] reported 2 cases of primary atypical pneumonia with autoagglutination of the red cells due to cold agglutinins, each of which developed an acute hemolytic anemia. These patients also had received sulfonamides, which the author believed was related to the mechanism of the hemolysis.

Stats and Wasserman,[4] in their excellent review of cold hemagglutination, mention a case of acute hemolytic anemia with high titers of cold agglutinins occurring during the course of primary atypical pneumonia. The patient had received sulfonamide, and the authors state that the exact casual relation between the pneumonia, the cold hemagglutination, the sulfonamide and the acute hemolytic anemia was not clear. They are of the opinion, however, that because of the parallelism between the titer of the agglutinin and the hemolysis the two are associated pathogenically.

Antopol et al.[8] described 2 cases of acute hemolytic anemia with autoagglutination following sulfonamide therapy, one of which was a pneumonia of questionable type treated with Neoprontosil.

The mechanism of the acute hemolytic anemia in these cases of primary atypical pneumonia with high titers of cold agglutinins is still not clear, but the presence of this phenomenon without sulfonamide therapy helps to clarify it somewhat. It can be stated that the hemolysis in such cases as the one reported here is not due to a combination of a high titer of cold agglutinins and injury of the red cells by sulfonamides, as Dameshek[3] thought. Rather, the hemolysis may be due to agglutination of the red cells in the peripheral vessels, resulting in stasis, the hemolysis taking place as a result of trauma. Stats[9] has caused hemolysis in vitro by mild trauma while using blood and fresh plasma with a high titer of cold agglutinins. The agglutinins themselves may injure the red-cell membrane and thus make them more susceptible to the factors of stasis and trauma.

The fact that many cases of primary atypical pneumonia with extremely high titers of cold agglutinins do not have hemolytic crises still remains a complete mystery.

Summary

A case of acute hemolytic anemia developing during the course of a severe primary atypical pneumonia that developed a high titer of cold agglutinins (autohemagglutinins) is presented. This patient received no sulfonamide therapy or treatment with any other drug that might have been the cause of the acute hemolytic process. Recovery occurred following repeated transfusions.

It is important to recognize that the pneumonias of the primary atypical type so prevalent for the last several years may develop a high titer of cold agglutinins that in themselves may be the cause of an acute hemolytic anemia as a serious complication.

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MEDICAL PROGRESS

HEMATOLOGY

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The Spleen

In its normal state, the spleen is a relatively small organ weighing 50 to 100 gm. and containing a variable amount of blood. Its function as a reservoir was thoroughly studied twenty-one years ago by Barcroft et al.[1] Removal of the normal spleen is followed by a number of interesting blood changes[2]— a tendency toward an increase in the red-cell count, the development of thin red cells (target cells) with increased hypotonic resistance, the development of Howell–Jolly bodies (nuclear remains) in the red cells and increases in the white-cell and platelet counts. These changes indicate a definite relation between the spleen and the blood-forming organs, notably the bone marrow, perhaps mediated by splenic hormones. The presence of red cells with nuclear fragments in the blood may indicate a splenic influence on denucleation of the red cell. Leukocytosis and thrombocytosis may be indicative of a spleen-granulocyte and a spleen-megakaryocyte relation. The development of thin red cells after splenectomy probably indicates that the mature red cells become thicker in their numerous but slow passages through the splenic sinusoids.

Although it is reasonable to assume that the spleen makes red cells thicker and thus prepares them for eventual breakdown so that they become more and more spherocytic, it is not known that the spleen actually destroys red cells. The old saying that the spleen is the graveyard of the red cells may require modification. Singer and Weisz,[3] by studying the bile excretion of normal and splenectomized dogs after phenylhydrazine hemolysis, demonstrated that there was no decrease in the output of bile pigment in the splenectomized animals. Thus, in dogs at least, and under the conditions of these experiments, it seems that the spleen has little if any influence on blood destruction. These results, so contrary to the long accepted opinions on this subject, must be confirmed in other animals and by different experimental methods before they can become completely accepted. The life span of the erythrocyte, as determined in these experiments, was approximately one hundred and ten days, in line with the more recent investigations on this point. Thus, it appears that less than 1 per cent of the red cells are destroyed daily. The actual process of red-cell destruction in the normal animal is but little known and may be simply a matter of increased spherocytosis and gradual wearing down (fragmentation).

The Spleen as an Endocrine Organ

The spleen is not ordinarily included among the organs of internal secretion. Nevertheless, more and more evidence — to be sure, largely of the indirect type — is accumulating that the spleen produces hormones that enter the blood stream and have effects on remote organs, notably the bone marrow. The recent series of observations of White and Dougherty[4] indicate a hormonal relation between the adrenal cortex and lymphoid tissue. Ungar[5] recently isolated from the normal spleens of guinea pigs a crystalline substance that he called "splenin" and that had the property of causing a reduction in the bleeding time, an increase in the capillary resistance and an inhibition in the release of histamine from blood cells. It was found that the spleen participated in the endocrine response

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to tissue injury and played a part in the control of protein metabolism. These results, although they require amplification and confirmation, are among the first clear-cut and direct bits of evidence indicating the presence of splenic hormones.

The relation of "splenin" to "thrombocytopen," described a number of years ago by Troland and Lee,[6] remains to be determined. It appears both from clinical studies and from the study of extracts of spleens removed from patients with idiopathic thrombocytopenic purpura that the spleen in this disease contains a material, possibly hormonal, that has distant effects on the production of platelets from the megakaryocytes of the bone marrow. Since the platelet count becomes and remains extremely high following splenectomy in the normal animal and human being, and since splenectomy in idiopathic thrombocytopenic purpura is followed by a dramatic increase in platelets, it seems reasonable to conclude that the spleen in this disease contains an excess of the normal platelet-regulating substance. Idiopathic thrombocytopenic purpura may therefore be a form of hypersplenism. The frequent presence of thrombocytopenia in patients with splenomegaly and the return of the platelet count to normal or above normal following splenectomy afford clinical confirmation of this concept. The results with the injection of splenic extracts from patients with idiopathic thrombocytopenic purpura have been inconstant, about half the investigators confirming Troland and Lee's original observations and half reporting no reduction in platelets. Recent experiments in our laboratory with dogs as the test animals indicate the presence of an active megakaryocyte-platelet inhibitor in splenic extracts from patients with the disease.[7]

Hypersplenism. The spleen normally exerts definite effects on the bone marrow, causing both quantitative and qualitative changes in the blood cells. These normal effects, however, seem to have little significance, since the splenectomized patient can live a healthy, normal life with no shortening of the life span. But under pathologic conditions the spleen may develop unusual importance and may even be detrimental to life. When the splenic physiology becomes abnormal, various effects that are concerned with the bone marrow and blood may ensue. The bone marrow produces three types of cells — red cells, granulocytes and platelets. The splenic or hypersplenic effects, so far as they can be determined, are anemia, neutropenia, thrombocytopenia and various combinations of these conditions. Hypersplenism may thus be selective or total. If total, pancytopenia is present.

Splenic thrombocytopenia is the best known of the forms of hypersplenism. In many cases idiopathic thrombopenic purpura occurs suddenly, but in others it is prolonged, with remissions and relapses. Recent studies of the bone marrow by Dameshek and Miller[8] show that platelet formation by the megakaryocytes is greatly reduced, but that following splenectomy it is greatly increased, leading to a rapid increase in the platelets in the blood. It appears that there is present in the spleen of patients with this disease an active material that causes inhibition of growth and delivery of platelets from the bone-marrow megakaryocytes to the blood. Thrombocytopenia may be primary or idiopathic, or it may be symptomatic of many conditions causing splenomegaly. Thus, in portal hypertension, — as in cirrhosis of the liver, — in disorders of fat metabolism (Gaucher's disease) and in chronic infectious splenomegaly the platelet count often becomes reduced, at times greatly so.

Splenic anemia has been discussed for years but has been largely discarded in the modern literature, chiefly because it became a blanket term covering many different disorders in which two features were present — anemia and splenomegaly. Many cases of leukemia, Cooley's anemia, sickle-cell anemia and so forth were called splenic anemia, until finally one investigator after another separated from this heterogeneous group different specific disorders. This left few conditions that could actually be designated as splenic anemia.

Abrami, De Gaudart d'Allaines and Dugas,[9] in a recent number of the French hematologic journal *Le Sang*, advocated revival of the term "splenic anemia" to include cases with splenomegaly and anemia in which splenectomy was therapeutically successful, apparently through the removal of an inhibitory effect of the enlarged spleen. Many cases of hemolytic anemia are cured by splenectomy. In some of these the red cells are defective; in a few, usually those in which the white-cell and platelet counts are also reduced, the spleen seems to be at the central point of the disease picture and splenectomy is dramatically successful. These cases are probably examples of hypersplenism with splenic anemia. Whether the spleen exerts only a hemolytic effect in these cases or also has an effect on maturation of red cells or their delivery from the bone marrow to the blood is not yet completely clear.

Splenic neutropenia is gradually becoming better known as a definite syndrome. This condition seems to be a form of hypersplenism in which the bone-marrow granulocytes are chiefly affected. First described by Frank[10] in 1916 under the term "aleukia splenica," the syndrome was revived more recently by Wiseman and Doan[11] under the designation "splenic neutropenia." Briefly, the combination of leukopenia, extreme granulocytopenia and splenomegaly is present. Pyogenic infections and fever are often present. Studies of the bone marrow rule out the presence of leukemia, lymphosarcoma and so forth and show increased numbers of granulocytes, despite the low granulocyte count in the blood. If the various studies and interpretations have been correct, splenectomy is followed by a

quick return to normal or better than normal granulocyte levels. Splenic neutropenia may be completely idiopathic — that is, the cause of the splenomegaly may be quite obscure — or may be associated with the splenomegaly of certain cases of rheumatoid arthritis (Felty's syndrome), Boeck's sarcoid, Gaucher's disease, tuberculosis of the spleen, malaria and kala-azar. In any of these conditions, and in others with splenomegaly, the neutropenia may become so severe as to lead to recurrent bouts of infection and fever. Patients with this syndrome often go from clinic to clinic without a definite diagnosis, with their lives frequently in jeopardy on account of the frequent development of pyogenic infections. Splenectomy has been extremely effective in an increasing number of cases. Recent reports include those of Langston, White and Ashley,[12] Rogers and Hall[13] and Salzer, Ransohoff and Blatt.[14]

Splenic pancytopenia or panhematopenia — the latter is a term recently used by Doan and Wright[15] — includes cases of splenomegaly in which there is a simultaneous reduction in all the cellular elements of the blood. Many patients with splenic neutropenia have more or less marked thrombocytopenia or anemia or both. In these cases it is of great importance to recognize that the pancytopenia is not due to aplasia or hypoplasia of the marrow but is brought about by an inhibitory effect of the enlarged spleen on the bone marrow; Doan thinks that a phagocytic effect is responsible. Many of these cases go unrecognized for years because either the spleen is not felt or the pancytopenia suggests the presence of a hypocellular marrow. Sternal-marrow studies reveal hypercellularity of all the elements, with large numbers of nucleated red cells, granulocytes and megakaryocytes. If the diagnosis and interpretations of the marrow picture are correct, splenectomy is usually followed by a quick return of the blood picture to normal.

These views, although relatively new, are being rapidly bolstered by increasing numbers of clinical cases. Together with the other bits of evidence, chiefly drawn from pathologic material, they strongly indicate the presence of splenic hormones having at times deleterious effects on the maturation and delivery of cells from the bone marrow to the blood. There is need for more direct evidence bearing on these points.

Rupture of the Spleen

With enlargement of the spleen in certain infectious states, notably in malaria and infectious mononucleosis, spontaneous rupture may occur, causing the symptoms of hemorrhage, shock and an abdominal emergency. Russ and Gaynor[16] report the case of a soldier who had had a single attack of vivax malaria overseas. Eleven months later, in this country, he developed a malarial chill that was accompanied by acute pain in the left shoulder, which radiated to and was localized in the left upper quadrant of the abdomen. Operation revealed a ruptured spleen and an abdomen filled with both fresh and old blood. Splenectomy was followed by recovery, but nine days postoperatively another chill occurred and *Plasmodium vivax* was recovered. Another case, also in a returned soldier, is reported by Kellner, Hochstein and Tillman.[17] In this case, shock quickly developed and the patient died before operation could be performed. At post-mortem examination, the abdomen contained 2500 cc. of fresh blood. The spleen was extremely soft and presented a transverse laceration in its midportion, together with several other small stellate lacerations. It is advised that great caution be observed in palpating for the spleen in an acute attack of malaria.

Although infectious mononucleosis is almost always a benign disease and is subject to few complications, it is occasionally accompanied by serious symptoms. In a case seen with Dr. A. Grassi, of Haverhill, severe thrombocytopenic purpura developed, requiring splenectomy. Reports of splenic rupture are increasing in number. Davis, MacFee, Wright and Allyn[18] report a typical case of the disease in a young man who was suddenly seized with sharp pain in the left upper quadrant of the abdomen and in the left shoulder and developed the symptoms of shock. At operation, a wide longitudinal split of the splenic capsule was found, together with two tears in the pulp. The splenic disease was typical of infectious mononucleosis. Recovery ensued. Other cases have been described by King,[19] Darley, Black, Smith and Good,[20] Ziegler[21] and Vaughan, Regan and Terplan.[22] Rupture in the last case took place with simple straining at stool. Martin[23] reports a case of ruptured aneurysm of the splenic artery.

Splenic rupture occurring spontaneously in an apparently normal spleen is reported by Duby.[24] A twenty-eight-year-old, married woman was suddenly seized with severe upper abdominal pain, difficult breathing and fainting. It was thought that she might have an ectopic pregnancy with rupture, and operation was therefore performed. Large amounts of intra-abdominal blood were found, and exploration revealed an enlarged, soft spleen with a large rent near the upper pole. Splenectomy was followed by recovery. The spleen weighed 340 gm. and showed multiple lacerations. No cause for the rupture was obvious, and the splenic histology was unrevealing.

Splenic Tumors and Cysts and Accessory Spleens

Bostwick[25] reviews the 157 cases of primary neoplasms of the spleen in the literature and adds 7 of his own. Seven types are discriminated: angioma — either hemangioma or lymphangioma; lymphoma; reticuloendothelial neoplasm; embryonic inclusions, including various types of cysts; fibrosarcoma; leiomyosarcoma; and neurosarcoma.

A report from Argentina by Unchalo, Mainetti and Cuculicchio[26] concerns an interesting case of a

young woman with fever, cough, weight loss and an enlarged spleen whose sputum contained the hooks of *Taenia echinococcus*. At operation, a large cyst replacing the spleen was found. Formalization and marsupialization were performed without splenectomy. Almost three years later, another abdominal operation was required and exploration disclosed complete absence of the spleen in the left hypochondrium, with a thick irregular process adherent to the diaphragm and the tail of the pancreas. There had been no recurrence of the hydatid cyst. Another interesting case report of a splenic cyst is that of Jameson and Smith,[27] who described a calcified cyst in an eighteen-year-old student complaining of left upper abdominal pain. X-ray films showed a partially calcified mass in the left upper quadrant, not connected with the stomach or the kidneys. Operation revealed an enlarged spleen that was replaced in large part by a calcified cyst. Splenic cysts are rare, only 152 cases of all types having been reported up to 1941; calcification has been reported in only 7 cases. In a case personally observed, a large mass in the upper abdomen, particularly prominent on the left, was thought to be of splenic origin because the white-cell count was low and contraction occurred following the injection of adrenalin. Operation disclosed an extremely large unilocular cyst, which was removed in toto, with complete recovery.

Accessory spleens may be an extremely annoying feature following splenectomy, particularly in idiopathic thrombocytopenia purpura and hemolytic anemia. Recurrences in such conditions may be due to the abnormal activity of such a splenunculus. Rhame[28] reports the case of a young man requiring abdominal operation whose spleen had been removed six years previously for traumatic rupture. Exploration revealed a tumor in the midjejunum under the serosa of the antimesenteric border of the bowel, impinging on the bowel lumen. Several similar smaller tumors were found along the greater curvature of the stomach and the lower margin of the transverse colon and in the greater omentum. Microscopically, all the specimens removed were hyperplastic hemolymph nodes, having the appearance of splenic tissue except for the trabeculae. It is considered that, in the young, splenic function may be restored after splenectomy, through hypertrophy of hemolymph nodes and by accessory splenic tissue. An unusual location for an accessory spleen is described by Olken,[29] who at autopsy in a fifty-six-year-old man who had died of a bleeding peptic ulcer found a tail of accessory splenic tissue that passed through the inguinal canal into the scrotum, where a bulb of splenic tissue was located.

Splenectomy

The indications for splenectomy are discussed in a series of letters in *Modern Medicine* for May, 1945. These letters were solicited in response to the abstract of an article by Carpenter[30] reviewed in the same publication in March, 1945. Dameshek classifies indications as absolute, probable and possible. The first are rupture of the spleen, idiopathic thrombocytopenic purpura, particularly if acute, familial hemolytic jaundice of the spherocytic variety if one or more crises have occurred, acute or subacute hemolytic anemia if a few transfusions have proved ineffective and if various specific causes for the increased hemolysis have been ruled out, and tumors and cysts of the spleen, if properly diagnosed. The *probable* indications include certain cases of splenic neutropenia, certain cases of Mediterranean sickle-cell anemia with unusual degrees of hemolysis and certain cases of splenic disease with pancytopenia. The *possible* indications comprise certain cases of chronic congestive splenomegaly, including cirrhosis of the liver and so forth, particularly those with leukopenia and thrombocytopenia. Doan, in the same symposium, lists the following indications: congenital hemolytic icterus, thrombocytopenic purpura hemorrhagica in which the marrow shows increased megakaryocytes, primary splenic neutropenia, primary splenic panhematopenia and any other type of splenomegaly associated with anemia or leukopenia, with or without thrombocytopenia. Doan's criteria for splenectomy are based essentially on the laboratory studies centered in sternal-marrow aspiration, with supravital studies of the removed cells, and the adrenalin test for splenic contraction. The latter, Doan believes, gives a biopsy, as it were, of the cells sequestered by the spleen. He thinks that in idiopathic thrombocytopenic purpura and splenic neutropenia the spleen sequesters cells rather than causing inhibitory effects on the bone marrow.

Cooley,[31] in the last article published before his death in October, 1945, described a new refractory hypochromic anemia, associated with elliptocytosis, which was unresponsive to liver and iron therapy and was present as a familial trait. There was apparently no Mediterranean or Negro admixture and no evidence of increased hemolysis. Splenectomy in 1 case resulted in slow, steady improvement. Cooley suggested that there is a group of anemias in which a defective type of hemoglobin or red-cell formation is present and in which there is a splenic influence on the bone marrow.

Pappenheimer, Thompson, Parker and Smith[32] report 3 cases of a severe form of hypochromic anemia, possibly hemolytic, not responding to liver or iron, in which splenectomy was performed. Two patients died of progressive anemia after splenectomy; in the third case the anemia was unchanged. Following splenectomy, all patients showed in the red cells small iron-staining coccoid or bacilloid bodies having a superficial resemblance to Bartonella parasites. It was concluded that the bodies were probably analogous to the so-called "siderocytes" previously described by Grüneberg.[33]

The Hemorrhagic Diseases

As in previous reviews, the following classification of the hemorrhagic diseases will be used, chiefly because it seems both simple and physiologically accurate. It is based on the thesis that loss of blood from capillaries is ordinarily controlled by an intact blood-vessel lining, by abundant platelets and by certain plasma constituents, such as prothrombin, fibrinogen and thromboplastin. Hemorrhagic diseases may therefore be classified as follows: vascular purpura, in which there is a disturbance of the blood-vessel wall; thrombocytopenic purpura, in which there is a greatly diminished number of platelets; and disturbances of blood coagulation — hemophilia, hypoprothrombinemia, fibrinopenia and so forth — in which a defect is present in one of the several blood-clotting factors.

Vascular Purpura

Bleeding into the skin in the form of ecchymoses and petechiae, unattended by a reduction of blood platelets, occurs under a variety of conditions — infectious or "toxic" — or for unknown cause. The large, purplish ecchymoses that have recently been so often observed in cases of meningococcemia are apparently due to the lodgment of meningococci in the skin capillaries and perhaps to some toxic influence on the blood-vessel walls. More frequent than these are the ecchymoses that many middle-aged women develop, particularly those with soft skins and rounded arms. These black-and-blue spots, often called "devil's pinches" because they occur spontaneously, usually appear in crops, chiefly on the thighs and arms. Their etiology is by no means obvious, although an endocrinal influence of some sort has been postulated. They have no particular significance and do not respond to vitamin, endocrine or other therapy. Of greater significance are the cases of vascular purpura in which crops of purplish ecchymoses occur about joints. These may be associated with renal disturbances. Histologic studies may disclose lesions resembling those of periarteritis nodosa. It is possible that such cases are related to such so-called "vascular" diseases as disseminated lupus erythematosus and periarteritis nodosa. There is evidence that the latter condition is a form of vascular allergy.

A blood-vessel disease that is familial and hereditary is hereditary hemorrhagic telangiectasia, first described by Osler, Rendu and Weber. Voyles and Ritchey[34] report 2 cases of this disease, which is characterized by the presence of multiple telangiectases, hemorrhage and anemia and a familial history. Their review of the literature disclosed 500 cases, occurring in about one hundred families. The hereditary factor is transmitted as a simple dominant and may affect either sex; atavism is occasionally noted. Epistaxes occur frequently, because the lesions that are often found in the nasal mucosa as well as in the skin and the mucous membranes consist of a dilatation of a blood vessel that is covered only by a very thin layer of epithelium. Cauterization, pressure packs, iron and transfusions have been used in therapy. Recently I have successfully employed packs of synthetic fibrin foam or absorbable sponge soaked in thrombin solution (bovine) to control the bleeding in such cases. Correll, Prentice and Wise[35] have recently described certain biologic investigations of the new absorbable sponge developed in the research laboratories of the Upjohn Company. This material has the attributes of fibrin and can be cut into any desired size or shape; it takes up solutions such as thrombin solution readily and can be molded to fit closely any bleeding surface. The pledgets gradually become absorbed and therefore do not require removal. Rundles[36] describes an unusual case of hereditary telangiectasia with epistaxis, bleeding from the gastrointestinal tract due to multiple gastric telangiectases, demonstrated by gastroscopy, and an aneurysm of the pulmonary artery. At postmortem examination, multiple small aneurysms of the splenic artery were also found.

Thrombocytopenic Purpura

Four types of thrombocytopenic purpura can be discriminated — that due to bone-marrow disease, in which the megakaryocytes are greatly diminished as part of a generalized disturbance, as in aplasia, leukemia, metastatic lymphosarcoma, fibrosis and so forth; that due to a local or selective bone-marrow disturbance in which a toxic, chemical or allergic disturbance affects the megakaryocytes and thus leads to a low platelet level; that due to the hypersplenic effects of an enlarged spleen (see above), as in cirrhosis of the liver, Gaucher's disease, chronic infectious splenitis and so forth; and idiopathic thrombocytopenic purpura, in which, although no splenic enlargement is present, there is probably a greatly disturbed splenic function.

Freeman[37] reports the case of a thirty-seven-year-old man with a long history of syphilis and antisyphilitic therapy. Because of a positive serologic test, mapharsen was given and was followed after ten injections by the development of purpura and death. The blood showed extreme anemia, neutropenia and thrombocytopenia. Another case of thrombocytopenic purpura due to mapharsen is reported by Schwartz and Vonder Heide,[38] who stress the benign character of the disorder and the lack of bone-marrow disturbance. These are not borne out in my experience. A case of sulfathiazole purpura is reported by Strong and Glassburn.[39] This patient had scarlet fever and was treated with sulfathiazole. After 19 gm. had been given, thrombocytopenic purpura developed. Scarlet fever per se is only rarely the cause of thrombocytopenia. Rappaport, Nixon and Barker[40] report the case of a thirty-seven-year-old man who was treated for rheumatoid arthritis with large doses of sodium

salicylate. The drug was discontinued and was resumed three weeks later. Severe hemorrhages ensued in association with a low platelet level. The megakaryocytes in the bone marrow were immature, with vacuolated cytoplasms and pyknotic nuclei. Splenectomy was performed, but the patient died. It is concluded that this was a case of allergic reaction to sodium salicylate with a direct toxic effect on the bone-marrow megakaryocytes. In the absence of any evidence of hypersplenism, splenectomy could hardly be expected to have had an effect in such cases.

Schwartz[41] describes the diagnostic and prognostic value of eosinophilia in the bone marrow in cases of thrombocytopenic purpura. He believes that if the eosinophils exceed an arbitrary base line of 50 in relation to 1000 leukocytes of the metamyelocyte-polymorphonuclear series, the thrombocytopenia is of an allergic nature and will improve spontaneously without splenectomy. With low eosinophil counts, however, spontaneous improvement is unlikely and splenectomy will probably be required. Although these conclusions are based on the analysis of a fairly large series of cases, 30 in all, they require confirmation. Nevertheless, the paper serves a highly useful purpose in directing attention to the possibility that certain cases of idiopathic thrombocytopenic purpura are allergic in nature. According to our own experience,[8] the megakaryocytes in idiopathic thrombocytopenic purpura are increased but platelet formation is greatly diminished. Following splenectomy, there is a remarkable increase in platelet formation by the megakaryocytes. When there is active bleeding, the postponement of splenectomy may prove disastrous, because of bleeding into vital structures. Carelli and Cangelosi[42] report a case of idiopathic thrombocytopenic purpura in which total blindness occurred, with active bleeding. Splenectomy performed when the bleeding had become quiescent was productive of a rapid increase in platelets, but no improvement in the optic atrophy occurred. This case points a valuable moral: although there is some danger in splenectomy in acute thrombocytopenic purpura, it is usually better to accept it than to adopt a waiting policy.

Disturbances of Blood Coagulation

Hemophilia. It seems likely that methods for keeping in check the dread disease hemophilia will shortly be available. The plasma-fractionation methods developed by Cohn and his collaborators at the Harvard Medical School have yielded an antihemophilic substance that has already been used experimentally by several groups of investigators. At the Thorndike Memorial Laboratory, where much work on hemophilia has already been done, Minot et al.[43] report on the effects of so-called "Fraction I" of plasma, which contains 60 per cent of fibrinogen, in 16 cases of hemophilia. In 15 of these, the intravenous or intramuscular administration of 11.5 to 125 mg. of the material was followed by a quick return of the coagulation time to normal. Fibrinogen alone is without effect. Intramuscular injections are at present associated with much pain. Further work on this and other fractions is awaited with much interest, and it may well be that before long the hemophilic patient will be able to give himself daily injections of the deficient plasma fraction and thus maintain his coagulation time at normal values.

Occasional cases resembling hemophilia occur in women. One such case is reported by Madison and Quick.[44] The patient had numerous serious hemorrhagic episodes. All the features in this case except one — the recalcified coagulation time — were identical with those of hemophilia. Quick had previously shown that the latter test is useful in differentiating a mild coagulation defect from true hemophilia. In hemophilia, the rapid centrifugation of oxalated hemophilic blood, followed by recalcification of the plasma, is productive of slow coagulation, whereas with slow centrifugation rapid coagulation occurs. In other hemorrhagic conditions, this difference does not occur.

Hypoprothrombinemia. The prolongation of the prothrombin time by the continued administration of salicylates was the subject of editorial comment in the *Journal of the American Medical Association.*[45] Salicylates in large doses appear to act in a fashion similar to that of dicumarol and may thus cause a reduction in circulating prothrombin. Severe cases of salicylate-induced hypoprothrombinemia may be associated with hemorrhage. Large doses of vitamin K may either prevent the development of prothrombin deficiency or hasten its disappearance. Pirk and Engelberg[46] found that quinine in ordinary dosage prolonged the prothrombin time, and suggested that the administration of vitamin K might be prophylactically beneficial in troops suffering bleeding wounds who were taking this drug. An example of the rare condition of idiopathic hypoprothrombinemia is reported by Austin and Quastler.[47] In this case severe and finally fatal hemorrhages took place. All other causes of hypoprothrombinemia — deficiency of vitamin K, hepatic damage and dicumarol poisoning — had been ruled out.

Hypothrombinemia continues to be utilized in some clinics as a prophylactic therapeutic method for the prevention of thrombosis following operation. Dicumarol, the active principle causing sweet-clover disease in cattle, causes prolongation of both the prothrombin and coagulation times. By careful observation of both these factors during administration of the drug, it is possible to maintain the coagulation times at high levels and thus minimize the dangers of thrombosis. The dangers of hemorrhage have, however, not been fully controlled. Jaques and Dunlop[48] noted that increases in the prothrombin time induced by dicumarol in rats could be shortened by adding calcium. This

may be of some therapeutic value when the blood prothrombin time becomes excessively increased with dicumarol therapy. Otherwise transfusions of fresh blood and large amounts of vitamin K are routinely used. Field and Link[49] found that the administration of large amounts of vitamin K protected rats against the action of dicumarol and in fact induced a temporary state of hyperprothrombinemia. Large amounts of 2-methyl-1, 4-naphthoquinone when administered to dogs, rabbits and rats were productive of hyperprothrombinemia lasting for several days. According to the observations of Spooner and Meyer,[50] dicumarol apparently not only affects the prothrombin time but also causes a reduction in platelet adhesiveness.

Fibrinopenia. The rarest form of coagulation defect is that due to fibrinopenia or fibrinogenopenia. Henderson, Donaldson and Scarborough[51] report such a case. The principal features of this hemorrhagic disease are its hereditary character, a high evidence of consanguinity in the parents, its presence in both sexes, a total absence of fibrinogen in the blood and complete incoagulability of the blood. The disorder is probably caused by a hereditary defect in fibrinogen formation. Acquired cases, in which the disorder is due to a toxic or neoplastic interference with fibrinogen formation by the liver and bone marrow, may occur.

Other disorders of coagulation. Pseudohemophilia is a hemorrhagic disorder that is occasionally encountered and that does not fit well into any one of the above groups. There is an increased tendency toward bleeding from minor wounds; the only constant defect found is a distinct increase in the bleeding time. The coagulation time may be slightly prolonged, and the recalcified clotting time may also be increased. The platelets are normal. Therapy by transfusions, splenectomy and so forth is without effect.

Evans and MacLaren[52] report the case history of a thirty-nine-year-old man who suffered bleeding from the skin, mucosa, and viscera. This disorder, they state, is a hereditary one affecting both males and females for at least four generations. No disturbances in coagulation time, bleeding time, prothrombin time or platelet count were present.

Penicillin and Blood Coagulation

Moldavsky, Hasselbrock, Cateno and Goodwin[53] studied the effect of penicillin on the coagulation, bleeding and prothrombin times in 20 patients. A marked reduction in coagulation time occurred in inverse ratio to the penicillin concentration. No change in prothrombin time took place. These authors suggest that penicillin is conducive to thrombus formation and may therefore be useful as a coagulant in certain hemorrhagic disorders. On the other hand, Hines and Kessler[54] found that penicillin sometimes caused a great increase in the effect of heparin in 2 cases of subacute bacterial endocarditis in which the latter drug was given as an adjuvant.

Influence of the Contacting Surface on Coagulability of the Blood

When blood is placed in a glass test tube, it clots normally in fifteen to twenty minutes, which is considered the normal coagulation time. It should be remembered, however, that this is an artificial method for determining coagulation, the blood vascular apparatus being something far different from glass. The smooth endothelial surfaces of the capillaries probably hinder blood coagulation. Tocantins[55] studied various materials from the standpoint of their effect on coagulation and demonstrated wide variations. For example, blood clotted much faster in glass than in the plastic lusteroid. This difference, which is greatly accentuated in hemophilic blood, is due, Tocantins concludes, to an excess of so-called "anticephalin" in the blood of hemophilia. He proposes this as another differential feature, particularly in mild cases of true hemophilia.

Anemia

A simplified classification of anemia was presented in last year's review.[56] Briefly, all cases of anemia may be divided into those due to a deficiency of the materials necessary for blood formation, — the deficiency anemias, — those due to a disturbed function of the bone-marrow production centers — aplastic and myelophthisic anemias — and those due to an increased loss or destruction of red cells — the hemorrhagic and the hemolytic anemias. A combination of this etiologic type of classification with one relating to cell size or color index is often useful in working out diagnostic leads, especially when it is realized that the anemia is merely a symptom indicating some sort of underlying disturbance.

Deficiency Anemias

Under the deficiency anemias are included liver-extract deficiency (pernicious anemia), iron deficiency, vitamin B deficiency and certain other conditions including sprue and tropical macrocytic anemia. In pernicious anemia, search has continued for the actual factor that is effective in relieving the liver-extract deficiency state. According to many recent reports, folic acid — a fraction of the vitamin B complex — may be the long-looked-for substance. One of the first reports in a medical journal on the use of this substance is that by Moore et al.,[57] who treated 2 cases of pernicious anemia with folic acid. Since then, many reports, official and unofficial, have shown conclusively that only a relatively few milligrams of folic acid are enough to induce a complete remission and maintain the blood counts at or near normal levels. A series of previous reports indicated that certain patients refractory to highly potent injectable liver extract might respond to the oral administration of large amounts of crude or proteolyzed liver extract. Thus, Watson and Castle[58] made observations on 3 women with nutritional macrocytic anemia; 2 of them were preg-

nant, and their cases would ordinarily have been classified as pernicious anemia of pregnancy. In all 3 cases, highly concentrated injectable liver extract was without effect, whereas large amounts of crude liver extract given orally were quite effective. Davis[59] reports somewhat similar observations in 3 cases of macrocytic anemia in children; proteolyzed liver given orally was rapidly effective. These observations are extended by Davis and Davidson[60] who successfully treated 15 apparently typical cases of pernicious anemia with oral proteolyzed liver after therapy with a parenteral liver extract preparation had proved unsuccessful. They conclude that proteolyzed — actually whole crude — liver contains a factor of hemopoietic value lacking in fractionated or concentrated liver extract. According to recent data, this unknown factor may be folic acid. The upshot of these several observations is that if one is reasonably certain that the macrocytic anemia in a given case is on a deficiency basis, therapy with either folic acid or crude liver extract should be used. Whether folic acid represents the entire answer to the therapy of pernicious anemia, and for that matter of all the deficiency states associated with macrocytic anemia, remains to be seen. This is particularly important with reference to the neurologic phenomena of pernicious anemia.

An important complication in pernicious anemia is the development of polyposis and gastric carcinoma. Polyps seem to form rather readily in the atrophied gastric mucosa of patients with the disease, and malignant degeneration of the polyps is fairly frequent. From a statistical study of 293 postmortem cases of pernicious anemia, Kaplan and Rigler[61] concluded that gastric carcinoma is three times as frequent in this group as in the general run of autopsied cases, the actual incidence being 12 per cent. It is suggested that frequent x-ray examination of the gastrointestinal tract be performed in cases of pernicious anemia.

The interesting pernicious anemia of pregnancy is discussed in an excellent and well documented article by Callender,[62] based on a study of 25 cases. Excessive vomiting or diarrhea suggesting toxemia of pregnancy is frequent. The patient is not usually icteric, and changes in the tongue often occur. The blood picture is by no means typical, but the bone marrow usually shows the characteristic megaloblastic appearance of liver-extract deficiency. The gastric juice generally shows free hydrochloric acid. In addition to these atypical features, most patients are refractory to liver extract, and transfusions are often required. It is already indicated that folic acid will become the therapy of choice.

Hemolytic Anemias

Life span of the red cell. A number of articles dealing with the longevity of the red cell have appeared. Callender, Powell and Witts,[63] by the method of differential agglutination, determined that the average life span of the human erythrocyte is one hundred and twenty days — that is, that 0.83 per cent of the circulation is replaced daily. Harne, Lutz, Zimmerman and Davis[64] studied the life span of the red cells of monkeys by observing reticulocyte showers after hemorrhage and found it to be ninety-four to one hundred and seventeen days. Singer and Weisz[65] studied the same problem in the erythrocytes of dogs by observing the output of bile pigment in biliary fistulas of the renal type. By this method the average life span was found to be one hundred and ten days. In another article, Singer[66] reviews the various methods for determining the life span of the red cell and suggests that determination of this factor may be important in studying hemolytic anemia. By methods of cross determination — that is, by studying the survival time of normal red cells in the patient's circulation and that of his red cells in a normal circulation — it would be possible to demonstrate in a given hemolytic disorder whether the fundamental defect lay in the red cell itself or was extracellular.

The maturation of reticulocytes within the circulation was studied by Young and Lawrence,[67] who injected 150 cc. of blood containing 73 per cent reticulocytes into a child with aplastic anemia. From all appearances, the reticulocytes matured within the circulation and were removed in about eight days. These results, the authors state, are to be accepted with caution in estimating the rate of red-cell regeneration and the life span of the normal erythrocyte.

Certain hemolytic mechanisms. Much is known of the fate of one of the red-cell constituents, hemoglobin, and of its conversion to bilirubin. Less knowledge exists, however, regarding the actual mechanisms by which the red cell itself is destroyed. It is not known whether it becomes swollen and bursts, is phagocyted by the ubiquitous reticuloendothelial system and the spleen or simply breaks down and becomes fragmented through the innumerable buffetings it undoubtedly receives in its many passages through the circulation. Many theories have been proposed, but none have been completely confirmed. Although it is probable that the spleen makes red cells thicker during their more or less lengthy sojourns in that organ, it is not entirely clear that the organ is the graveyard of the red cell. A similar criticism holds for the reticuloendothelial system, which many writers so glibly refer to as the site of red-cell destruction. Somehow, the chemical concepts dealing with lecithin and "lysolecithin" hemolysis are not highly convincing. It is possible that other simpler and more mechanical principles have to do with red-cell destruction. These may include erythrostasis in various organs, including the spleen, the effects of mechanical trauma and the inevitable ageing of the red cell.

Various mechanisms dealing with abnormal red-cell destruction, about which more is known, have

been cited in previous reviews. These include the effects of hemolysins, agglutinins, certain chemical factors and such physical factors as heat and mechanical trauma. Dameshek and Miller[68] demonstrated that red cells that are acted on by various types of agglutinins become more vulnerable to the effects of mechanical trauma than are normal erythrocytes — that is, their mechanical fragility is greatly increased. Stats and Wasserman[69] later showed that the cold hemagglutinin resulted in hemolysis when the cells were subjected to trauma. In further studies, Stats[70] states that no clear understanding of the role of mechanical trauma in normal or abnormal red-cell destruction is at hand. Shen, Castle and Fleming[71] also studied the factor of mechanical fragility and have shown that an increased fragility occurs in the presence of agglutinins, in sickle-cell anemia and in certain cases of congenital hemolytic jaundice. They concluded that mechanical fragility is probably a factor in certain hemolytic processes.

Hereditary hemolytic anemias. Three types of hereditary hemolytic anemia may be discriminated — spherocytic (congenital hemolytic jaundice), Mediterranean target-oval cell (Cooley's anemia, Mediterranean anemia) and African target-sickle cell (sickle-cell anemia). The Mediterranean type, associated with leptocytosis — thin or target cells — has recently come to the fore as a type frequently seen in persons of Italian, Greek, Syrian and Portuguese ancestry. Dameshek[72] has discriminated severe, moderate and mild types, the severe type having been known for years as Cooley's anemia. Despite the low color index, there is no response to iron therapy. Neel and Valentine[73] have made comprehensive studies of the disease in the rather large and homogeneous Italian population of Rochester, New York. They divide the condition into two types — thalassemia major and thalassemia minor. The major type occurred in 1 of 2368 births; the minor type was present in 1 of each 25 Italians tested. According to their figures, about 4 per cent of all Italians show hypochromic anemia or erythrocytosis, target or elliptical cells or both and increased hypotonic resistance of the red cells. Stippling of the red cells is a prominent feature and may lead to the incorrect diagnosis of lead poisoning in a patient who has been exposed to this metal. Many cases of Mediterranean anemia show more elliptocytosis than leptocytosis.

Target cells or leptocytes, which are unusually thin and are therefore unusually resistant to hypotonic salt solutions, are a prominent feature in both Mediterranean anemia and sickle-cell disease. Their presence in these conditions is probably indicative of an inherent fault in hemoglobin metabolism or perhaps the lack of an additional factor necessary for the complete synthesis of hemoglobin. Valentine and Neel[74] produced target cells in vitro by suspending normal erythrocytes in plasma or serum rendered hypertonic by evaporation or by the addition of sodium chloride or potassium oxalate. Furthermore, target cells from a case of sickle-cell disease were converted to normal-appearing red cells by suspending them in plasma rendered hypotonic. The significance of these observations is not entirely clear.

Sickle-cell anemia shows many target cells in the stained blood-smear preparations. This immediately brings up a possible relation between this disease and the Mediterranean syndrome. Many points of similarity are present, and forms intermediate between the two diseases are at times discriminated. Such a possible intermediate form may be that observed by Wagner[75] who found 86 per cent ovalocytes in a healthy Negro donor. No sickling was present. I have seen occasional target-cell and oval-cell cases in Negroes without sickling. The entire subject, particularly with reference to hereditary features, needs amplification. Scherer and Cecil[76] report a case of typical familial spherocytosis in a Negro. They state that this type of congenital hemolytic jaundice has been reported only once before in a Negro. As Negro blood becomes more and more diluted by intermarriage with other races, it is possible that the incidence of the spherocytic type will increase.

Cooley[77] described an anemia observed in two brothers of non-Mediterranean (Dutch) ancestry that appeared to be transmitted in a sex-linked manner similar to that of hemophilia. Striking elliptocytosis was present, in association with microcytosis, hypochromia, erythrocytosis and splenomegaly. The oral and intravenous administration of iron was without effect. Splenectomy was performed in one of the patients with only a partial response, although many of the elliptocytes disappeared. Cooley concludes that there is an inherent defect in hemoglobin synthesis unaffected by splenectomy.

A case of hemolytic anemia in infancy, possibly congenital or possibly acquired, is reported by David and Minot.[78] During a hemolytic crisis the patient's serum showed the presence of an autohemolysin and an isohemolysin, which disappeared after splenectomy. The patient made a full recovery and behaved in most respects like most patients with acute hemolytic anemia of the acquired type. James and Evans[79] report a case of acquired hemolytic jaundice having its onset at the age of seventy and cured by splenectomy. Fourteen similar cases in patients aged fifty or over are discussed; five showed improvement after splenectomy. The risk of splenectomy in the elderly patient is naturally much higher than it is in the young one; acceptance of this risk is nevertheless essential if even one third of the patients are to be saved.

Hemolytic anemia that is secondary or symptomatic of a more fundamental disorder is occasionally seen. This occurs most frequently in Hodgkin's disease, lymphosarcoma and lymphatic leukemia, particularly when the spleen is greatly involved.

In rare cases a dermoid cyst, usually of the ovary, is associated with severe hemolytic anemia.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32251

PRESENTATION OF CASE

A fifty-two-year-old widow entered the hospital for study of a lesion in the left upper lobe of the lung.

Six years before admission a panhysterectomy had been performed on the patient at another hospital for carcinoma of the fundus of the uterus. Pathological examination revealed a pedunculated papillary adenocarcinoma of the fundus, with minimal invasion of the myometrium. After operation she was observed frequently until two months before admission, with negative results; at this time she had a cold, with a productive cough during which one sputum sample was blood streaked. A circumscribed area of increased density, 2 cm. in diameter, had appeared in the base of the left upper lobe of the lung. Tubercle bacilli could not be demonstrated in the sputum. The cough disappeared shortly, but the lesion in the lung remained. There were no further hemoptyses, and she was asymptomatic at the time of admission.

Between the ages of forty-one and fifty the patient had frequently been observed at a sanatorium following the death of her husband from tuberculosis. At first there was a small area of productive infiltration in the first right interspace, which gradually cleared during the period of study. No lesion was ever seen in the left lung. There was also a long history of moderately severe hypertension, with one episode of dyspnea and ankle swelling. She had several anginal attacks over a period of many years. Four years before admission a right pyelotomy for renal calculi was performed.

On physical examination the vagina was deep, and there was a well suspended vaginal cuff. The cervix and uterus were not palpable. The vaults were clear, and rectal examination was negative. The cardiac rhythm was irregular, and a blowing systolic murmur was heard at the apex. The lungs were clear.

The temperature was 98.6°F., the pulse 80, and the respirations 16. The blood pressure was 190 systolic, 115 diastolic.

There were 14 gm. of hemoglobin. The white-cell count was 8000. A rounded area of increased density 2 cm. in diameter was visible in the chest film just opposite the anterior end of the fourth left rib in the basal portion of the upper lobe (Figs. 1 and 2). X-ray examination of the skull, pelvis and long bones was negative. In the intravenous pyelogram 58 per cent of the dye was excreted in sixty minutes. The right renal pelvis as seen by retrograde examination was reduplicated. The lowermost group of calyxes was less blunted than those in the upper group. The superior calyxes were represented only by large, somewhat irregular cavities. A distinct defect consistent with an aberrant vessel was seen between the somewhat widened upper ureter and the pelvis. The calyxes on the left were normal, but the pelvis was large. The ureter was normal. Ten red cells and rare white cells per high-power field were found in the right kidney urine sediment, and occasional red cells and three white cells per high-power field in the left.

An operation was performed on the thirty-first hospital day.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI: "An operation was performed on the thirty-first hospital day." The record does not say what kind of operation, whether it was on the kidney or the lung, but I suppose that it was performed on the lung.

Apparently I have been given the task of answering the time-honored question of the cause of a round shadow in the lung. Before we come to that, let us analyze the rest of the patient's history. We know that she had hypertension and angina. I do not believe that these need concern us at all. She had lesions of her kidneys. We had better look at the pyelograms. The intravenous and retrograde examinations were performed in a two-week interval. The films demonstrate what the record says — that both kidneys function and both look abnormal, the right more than the left. On the right side the kidney pelvis is bifid. The lower part of the bifid pelvis shows the dilatation frequently seen with an aberrant vessel. At the ureteropelvic junction one can see a defect that fits that diagnosis. The upper part of the bifid pelvis is not dilated, but there are large sacs representing markedly dilated calyxes. On the left side, the calyxes are fairly normal. The kidney pelvis itself shows some dilatation, which is not too remarkable. The appearance of the right kidney is consistent with what one sees in an aberrant vessel with extensive infection in the upper half of the bifid pelvis. We can say that this patient had pyelonephritis in the upper half of the kidney. Could this be tuberculous pyelonephritis? Since the patient was exposed to tuberculosis, I think that it could be, but a few facts make it a little unlikely. The first is that a number of years

before admission she had a pyelotomy and stones were removed from that kidney. Tuberculosis would probably have been diagnosed at that time. In addition, the kidney condition on admission was asymptomatic. That does not rule out tuberculosis, but tuberculosis is less likely than nonspecific pyelonephritis.

Another pathologic condition was a round mass in her lung. The two x-ray examinations were done six weeks apart, and the shadow did not change. On the lateral view the lesion seems clearly to lie in the lower portion of the left upper lobe. The heart to the left. The hilar shadows do not look abnormal, and they are in normal position and of normal size. There is one helpful fact in the history: the patient apparently had a negative chest film two years prior to entry. At least that is what the record states. For the sake of discussion we shall assume that the interpretation was correct, which would automatically exclude a number of congenital lesions, or some slowly growing lesions. In other words, there was a round mass, which developed in two years. This lesion was first discovered when the patient had a so-called "upper

FIGURE 1. *X-Ray Film of Chest.*
The arrow points to a rounded area of increased density.

shadow is not quite round in the only lateral view that we have here. In addition to this finding I see two more abnormalities, which are not described in the record and which indicate that there is a slight decrease in the size of the left lung somewhere. On the lateral view there are a few streaks in the region of the lingula of the left upper lobe, which are less distinct in the anteroposterior view. The right lung, which normally extends posteriorly to the region of the spinous process, extends almost to the left edge of the spine, indicating that the right lung is too large and the left lung too small. In addition there seems to be a slight shift of the respiratory infection" and had some blood-streaked sputum. The slight decrease in the size of the lung could conceivably be the residue of atypical pneumonia, which she might have had at that time, and could be merely a red herring so far as the lung lesion is concerned. Could the patient have had an infarct two months previously, of which this was the residue? The round mass lies in the middle of the lobe and not against the pleural surface, which automatically excludes an infarct.

If one leaves out queer and unusual things, one is left with three possibilities: tuberculosis, metastatic cancer and primary cancer of the lung. This

patient had been exposed to tuberculosis. Tuberculosis can produce a round single lesion in the lung. More frequently in the primary phase, but also in the reinfection type of tuberculosis, single or multiple round lesions are seen. From a roentgenologic viewpoint this could be tuberculosis. The exposure was many years back, the patient had repeated examinations in between showing a negative chest film, and the location was rather unusual for primary or reinfective type of tuberculosis, but still this may have been tuberculosis.

FIGURE 2. *X-Ray Film of Chest.*
The arrow points to a rounded area of increased density.

The patient had a carcinoma of the uterus removed six years before entry. Could this lesion in the lung be a metastasis? Cancer of the uterus may metastasize to the lung, and metastases may appear in the lung at such a late date, even though the primary tumor has been removed. How about the small hematemesis that the patient had? Can metastases produce bleeding? Yes; they can. Dr. King and Dr. Castleman* have published some cases of involvement of the bronchial tree by metastatic tumor causing hemorrhage. If we assume that this lesion was metastatic, we must forget what we said about the decrease in the size of the lung. I assume that had nothing to do with the present lesion, which could be a metastasis.

Could this woman have had a primary tumor of the lung, a bronchiogenic carcinoma? It would be just about the smallest I have seen, but that is because we probably have not heretofore operated on them at that stage of the game, whereas we now do, owing to the marked development of chest surgery. In years past we should have enumerated the possibilities that we are talking about now and said, "Let us watch." This could be a very small primary carcinoma of the lung, more or less in the periphery.

I am ending up where I usually end up with a single round lesion in the lung. From purely roentgenologic evidence, it is often impossible to make a differential diagnosis. This picture could be explained by any of the three possibilities that I have mentioned. That is my answer as a roentgenologist. As a clinician, I should probably take a guess, and I shall say that it was a malignant tumor.

DR. EDWARD B. BENEDICT: Would you consider a metastasis from a kidney tumor?

*King, D. S., and Castleman, B.: Bronchial involvement in metastatic pulmonary malignancy. *J. Thoracic Surg.* 4:305-315, 1943.

DR. SCHATZKI: I should consider metastases from any tumor. We have the old one, adenocarcinoma of the uterus. I do not see a primary tumor of the kidneys in the films.

DR. JOE V. MEIGS: Is it not unusual for a patient with carcinoma of the endometrium, a papillary type, without much invasion of the myometrium, to have metastases six years later? Most patients who have that sort of cancer do not have recurrences and metastases.

DR. DONALD S. KING: I hope it is not cancer because if it is we must do a great deal of operating. It may be cancer and I should not want to be the one to say it is not. The case that I have to discuss in a moment is something of the same problem, and I brought down slides on 3 other cases that are waiting for a decision on this type of shadow. These 2 cases this morning will help us in making our decision. I shall guess that the diagnosis in this case is tuberculosis.

DR. F. DENNETTE ADAMS: What about bronchoscopy?

DR. TRACY B. MALLORY: The lesion was so far out in the periphery that it was not helpful. I do not know whether Dr. Benedict expressed an opinion about this beforehand.

DR. BENEDICT: We were of the opinion that it would not show anything.

DR. NICHOLAS MARTIN: What about the possibility of adenoma of the bronchus?

DR. SCHATZKI: I do not believe that we have had a single benign adenoma of the lung that has not produced fairly marked bronchial occlusion.

DR. MARTIN: I disagree — not absolutely, but I think it does occur.

DR. RICHARD H. SWEET: Before we discuss it any further might we not ask this question: Is it not true that adenomas are related to the large bronchi?

DR. MARTIN: Yes.

DR. SWEET: We have had one benign adenoma that was not in a large bronchus.

DR. MARTIN: I still think we have to list it as a possibility.

DR. SCHATZKI: Would not the negative x-ray examination two years previously be against benign adenoma?

DR. MARTIN: Yes; that is a better reason.

DR. SWEET: Dr. Schatzki and Dr. King brought up what I consider an important point, namely, the utilization of surgery in some of these cases to make a diagnosis as well as to carry out treatment, because thoracic surgery is now on such a sound basis that we can operate in cases of this sort with a negligible risk. In recent years we have explored many of these patients whom, as Dr. Schatzki said, we used to watch. Our preliminary diagnosis was tumor, probably metastatic. I was impressed, as Dr. King and Dr. Schatzki were, by the fact that if it was a primary carcinoma, it was certainly a very small one, smaller than any that I can recollect.

There was another factor that made the case interesting — the patient entered with the complaint of hypertension. Dr. Smithwick was asked to see her about the possibility of treating the hypertension surgically. The question arose whether she might have the first stage of sympathectomy done at the same time as the lung operation. That was the question put to me. I did not see her until late in the course of the study. I was opposed to combining the two procedures because I believed that the tumor in the lung was of greater importance to this patient from the standpoint of length of life than the hypertension. I agreed that, if it turned out to be a simple procedure, we might do a transthoracic exploration. We explored her and found an anomalous upper lobe. The peculiarities that Dr. Schatzki mentioned are explained, I think, on an anatomical basis, because she had a lingula with an almost complete fissure. That fissure was subdivided to correspond to the two branches of the lingular bronchus. It was a peculiar looking lingula. At the base of the proximal portion of one of the lingular segments was a tumor, which was obviously neoplastic. We thought first of doing a lingulectomy, but it was so close to where I had to resect that I decided that the safer and more conservative procedure was to do a left upper lobectomy. Because it was a simple operation, I allowed Dr. Scannell, after I had completed the lobectomy, to do a sympathectomy, which he did, and the patient made an excellent recovery.

CLINICAL DIAGNOSIS

Tumor of lung, probably metastatic.

DR. SCHATZKI'S DIAGNOSIS

Malignant tumor of lung.

ANATOMICAL DIAGNOSIS

Pulmonary metastasis from adenoacanthoma of uterus.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The crux of the diagnosis rests on the histologic examination of this tumor. It was quite small, 2 cm. in diameter, and very well circumscribed. A small bronchus ran into and terminated in the tumor, and the mucosa of this bronchus was slightly roughened by invasive tumor at the point of contact. On microscopical examination the tumor proved to be an adenocarcinoma, with a number of foci of squamous-cell metaplasia, the type of tumor ordinarily called an adenoacanthoma. This is a relatively frequent type of tumor in the uterus, much less usual in any other organ, and I cannot remember ever having seen it as a form of primary bronchiogenic carcinoma. We were eventually able to borrow a slide of the original uterine tumor and found that it also had the characteristic appearance of an adenoacanthoma. On that

basis, we are on safe grounds in assuming that it was a metastasis from the uterus, which had been resected seven years previously.

CASE 32252

Presentation of Case

A thirty-two-year-old housewife entered the hospital for study of a mass in the right lung.

One and a half years before admission the patient entered another hospital because of headache and weight loss. An area of density 3.0 by 2.5 cm. was visible by x-ray in the right lower lobe. It was smooth in outline and homogeneous in density. The lung fields were otherwise clear. There had been no cough or hemoptysis. Bronchoscopy was negative. The patient refused operation and was discharged. During the next year and a half she was constantly fatigued, but lost no more weight. The headaches became less frequent and severer. The attacks were often associated with dizziness and mild nausea. Mild exertional dyspnea appeared in the last six months. One month before admission a mild hacking, nonproductive cough developed. There was no fever or sweating at night.

With the birth of a son thirteen years prior to admission, the patient had had "milk legs," which kept her in bed nine weeks. Early in this period there was a sudden, sharp, pleuritic pain anteriorly in the left chest. This lasted a day and caused difficulty in breathing.

A cousin with whom the patient had close contact died of tuberculosis eight years before admission. At the age of twenty-four the patient had a bilateral salpingectomy. The pathological report was acute bilateral salpingitis. The periods thereafter were regular until admission, lasting from one to six days. The first day of the period was usually accompanied by cramping pains.

On physical examination there was a decrease in breath and spoken voice sounds over an area 4 cm. in diameter to the right of the spine over the right lower lobe. The heart was normal. There was a healed midline suprapubic scar, with an area of slight tenderness around it. The cervix was long and normal. The uterus was forward and attached to the abdominal wall, was larger than normal and felt round. A hard, firm, irregular mass was palpated along the right side of the fundus.

The temperature was 99°F., the pulse 72, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

The red-cell count was 4,180,000 with 12.7 gm. of hemoglobin. The white-cell count was 7700, with 57 per cent neutrophils. The urine was normal. X-ray examination of the lung revealed a mass just below the right hilum, probably in the right lower lobe. It had not changed in appearance from the original film. A flat plate of the abdomen and an intravenous pyelogram showed normal urinary tracts. There was an ill defined, irregular mass in the pelvis slightly more to the right than left measuring approximately 11 x 6 cm. in diameter. It did not appear to exert any pressure on the urinary tract. A barium enema was negative.

An operation was performed on the twelfth hospital day.

Differential Diagnosis

Dr. Donald S. King: As Dr. Schatzki said in the preceding case, we are constantly faced with the problem of what to do with cases that show, in the x-ray film, a small rounded area of density in the lung field. Within the last three weeks we have seen such shadows in 3 cases, similar to the one that is presented to me today. I should like to put up the films on these 3 cases along with the film of the case that I am to discuss. The first film is the film of today's case. Unfortunately there is only a Bucky film, which does not give the same density as an ordinary film. The lateral film in this case is also shown. As one notes, the 3 other cases are different from the case under discussion in that the lesions are in the peripheral areas of the lungs and are not near the hilum. The first of the outside patients had a negative x-ray film in 1939. An x-ray film taken in 1942 showed the rounded lesion. Fortunately I was away at the time that this film was taken and did not have to decide whether anything should be done about it. We have other films taken in 1944 and 1946, which show that the lesion had changed very little if at all. The second case was one in which the lesion was picked up by routine examination of all the employees of one of the large Boston department stores; there were no symptoms of pulmonary disease. In the third case there were definite pulmonary symptoms, and the decision to operate will probably not be difficult.

In the discussion of today's case we note first the story of pleuritic pain that lasted a day and caused difficulty in breathing. There seems little question that the symptoms were due to a pulmonary infarct. I do not believe that there is any association between this episode and the rounded shadow that appeared some years later.

As in the case discussed by Dr. Schatzki, this patient was also exposed to tuberculosis, and the diagnosis of tuberculosis must therefore be considered. There is a possibility that the bilateral salpingitis was also of a tuberculous nature, but I assume that a pathological report of acute salpingitis rules out tuberculosis. Am I right in this, Dr. Meigs?

Dr. Joe V. Meigs: Yes.

Dr. King: "There was a decrease in breath and spoken voice sounds over an area 4 cm. in diameter to the right of the spine." This examiner certainly made a careful examination. I shall wager anything that he had seen the x-ray films before he made that report.

I assume, from the description of the pelvic examination, that there were two masses, one of which was the uterus itself and the other outside the uterus, but I cannot be absolutely sure of this from the description given.

The most important sentence in the whole history of the case is in the x-ray report, which reads, "It had not changed in appearance from the original film." We are therefore dealing with an x-ray lesion that did not change in one and a half years. The X-ray Department goes on to report, "An intravenous pyelogram showed normal urinary tracts." Obviously the doctors in charge of the case were looking for evidence of a hypernephroma from which there had been a solitary metastasis to the lung.

I suppose again, as in Dr. Schatzki's case, that the operation performed was an operation on the lung and not on the pelvis, and that we are again faced with the question of the nature of the round shadow. My first inclination was to bet again on tuberculosis because of the story of exposure and because the symptoms were somewhat suggestive of a tuberculous infection. But there are two things against this diagnosis. In the first place, with a small rounded shadow that is due to tuberculosis, there is usually evidence of tuberculosis elsewhere in the lungs. This is, however, not necessarily true. In the second place, except in a calcified primary complex, the rounded shadows due to tuberculosis, or so-called "tuberculoma," usually change in appearance in eighteen months' time. I believe that almost all the tuberculomas that we have observed have changed in the x-ray film in this length of time. Am I right, Dr. Sweet?

DR. RICHARD H. SWEET: Yes; I agree.

DR. KING: I am therefore inclined to say that the lesion under discussion is not tuberculosis.

As I noted in the beginning, this rounded shadow is near the hilum of the lung where we have seen some bronchiogenic cysts, and some of the smaller cysts in this area have given somewhat similar x-ray appearance. Usually, however, the area of density is larger and gives a somewhat different shadow. I do not believe that this picture is sufficiently characteristic of a bronchiogenic cyst to warrant such a diagnosis.

Primary carcinoma of the bronchus and metastatic cancer are both, I believe, ruled out by the fact that there was no change in the appearance of the x-ray film in a year and a half. So far as our experience goes I do not believe that there has been a single case of primary or metastatic cancer of the lung in which the x-ray shadow has not changed in this length of time. Even the hypernephromas, some of which are very slow growing, have changed definitely in that time.

Of course I am concerned about the condition in the pelvis. As I went over the case I was about to forget that there was anything wrong there, and until the discussion of Dr. Schatzki's case I had not given a thought to the possibility of a pulmonary metastasis from the pelvis. Assuming that the operation was on the lung, it is quite obvious that the doctors in charge did not believe that there was pelvic cancer from which a metastasis might occur. But I should like to have Dr. Meigs discuss the possible diagnoses of the pelvic mass.

DR. TRACY B. MALLORY: You are wrong about that. The operation was on the pelvis.

DR. KING: This is, of course, a bombshell. I was going to forget the pelvic disease so I am even more interested in what you think about the pelvis condition, Dr. Meigs.

DR. MEIGS: I have a note on the record that I shall try to find.

DR. FLETCHER H. COLBY: I am not convinced that metastatic lesions in the lungs necessarily change, as you say, in a brief period. I do not know about one and half years.

DR. KING: The only ones that I can be sure about are the ones that I have followed personally, and as I said, all of these have increased in size in a few months. In the famous case of hypernephroma[1, 2] in which the kidney was first removed and the metastasis taken out several months later, with apparent cure after twelve years, the metastatic lesion had almost doubled in size in a year's time. We have also recently followed a case in the Baker Memorial Hospital in which the hypernephroma was taken out five years ago and metastatic lesions appeared in the lung one year ago. The lesions in the lung have unmistakably increased in size during the year's observation. What the chest x-ray films might have shown if they had been taken in the four-year period before the metastatic lesions were discovered, I do not know.

DR. COLBY: Some are fairly slow in growing. They must be, because secondary deposits may appear even as late as fifteen years or more.

DR. KING: I am going on the basis of my own experience in tumors like this.

DR. MEIGS: I shall read part of my note. "The cervix is long and normal in appearance. The uterus is forward and attached to the abdominal wall; it is large and round — definitely larger than it should be. The left side is negative, but in the right side I believe I feel a hard, firm, irregular mass. This mass probably represents the right ovary, although with tumor in the lung I think we ought to consider that that might be a question of neoplasm. Dr. Benedict should be asked if he would like to peritoneoscope her. If he does not, and all studies on your Service are negative, we would be very glad to explore her."

The question is, What kind of mass is it? Apparently she had no abnormal menstrual periods. One would have to consider the possibility of a fibroid growing off the side of the uterus. It might be in the form of leiomyosarcoma, which is a malignant tumor and may metastasize to the lung. Pelvic

inflammatory disease we rule out because she had had both tubes removed. One would have to consider ovarian tumor, and it could even be endometrial cancer.

DR. KING: I should not have Dr. Meigs do my work for me, but I think it is fair under the circumstances.

We do not know what this lesion in the lung was then?

DR. MALLORY: Yes; we do.

DR. KING: And you know what the pelvis showed too?

DR. MALLORY: Yes.

DR. KING: I am now faced with the question of whether we can connect the two processes. I came determined not to consider the pelvis as a possible source of metastasis, and I shall keep to that line of approach. I do not believe that this is metastatic cancer, and I have already discarded tuberculosis and bronchiogenic cyst. The question that was raised about benign adenoma in the previous case interests me a great deal. Until 1942, except for one possible case, all the adenomas that we had followed were at least in part in the lumina of the larger bronchi and could be definitely proved by bronchoscopic biopsy. I had been told that while I was away there was a case admitted from another hospital in which operation had shown an adenoma that was entirely outside the bronchus. The case under discussion may be that case. I do not know. In view of the fact that this lesion has not changed in x-ray appearance in a year and a half and that it is close to the large bronchi, adenoma must be considered as a possible diagnosis.

There are a multitude of other benign tumors that should be mentioned, but it would be pure guesswork to try to name any other tumor. Fibroma, chondroma and hamartoma are all possible, but taking everything into consideration since I have to commit myself as to diagnosis I should say adenoma.

CLINICAL DIAGNOSIS

Adenoma of bronchus.

DR. KING'S DIAGNOSIS

Benign adenoma of lung.

ANATOMICAL DIAGNOSES

Adenoma of bronchus.
Endometriosis of ovary.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The first operation was on the pelvis, and an ovarian mass was found to be due to extensive endometriosis of the ovary. About ten days later the chest was explored, and Dr. Sweet will now tell about that.

DR. SWEET: This patient was admitted on the gynecological service, and I was asked to see her before the pelvic operation relative to what was wrong in the chest and whether anything should be done. I thought we had better see what was in the pelvis first because at that time we did give some thought to metastatic tumor. Having proved that the pelvic tumor was benign and therefore not responsible for the pulmonary lesion, we did go ahead with the chest operation. My reasoning was exactly the same as Dr. King's, and I came to the same conclusion on the same premise — that it was an adenoma. It was an interesting operation because when I first exposed the tumor it was in the lower lobe, presenting on the fissure as it lay against the middle lobe. I thought that I could excise the tumor locally. There was not much lung tissue over it. I believed that it was something I could pry out without difficulty, but in dissecting I saw that it was actually growing out of a bronchus and did a lobectomy. The further pathologic details we shall hear from Dr. Mallory, but I was convinced at the time that I was taking out an adenoma.

DR. KING: Was it inside or outside?

DR. SWEET: Both.

DR. MALLORY: I have the gross picture of the resected specimen. You can see the tumor without any difficulty, almost completely circumscribed, but as Dr. Sweet explained it was definitely adherent to the outer portion of the bronchial wall. There was no involvement of the bronchial mucosa and no narrowing of the bronchus by tumor. These tumors ordinarily arise within the bronchus, although they may also extend outward between the cartilages and form a dumbbell-shaped mass. This is a unique case, in our series at any rate, in that the tumor lay entirely outside the bronchus, with no projection in the bronchial lumen.

DR. MEIGS: This patient had bilateral salpingitis and endometritis eight years before admission. It is rare to see endometriosis under such conditions when the tubes are closed. This seems to refute Sampson's theory of menstrual blood flowing back through the tubes and producing endometriosis. If she had had the condition when she was first operated on it would probably have been noted.

DR. MALLORY: You might have noted it, but most surgeons do not see it as readily as you do.

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TO THE MEMORY OF WALTER B. CANNON

Elsewhere in this issue of the *Journal* is a description of the Walter B. Cannon Memorial Hospital Fund. It is the purpose of this editorial to draw attention to this enterprise, and to point out how near the work to which this fund is to be devoted was to Dr. Cannon's heart.

For a number of years Spanish students worked intimately with Dr. Cannon in his laboratory, and when the lamentable overthrow of liberalism occurred in Spain, their continuing relation was greatly curtailed. Dr. Cannon had an instinctive, almost puritanical justice in his make-up, which overflowed with especial forcefulness when intellectual freedom suffered, particularly when the sufferers were imaginative young men.

If life had been spared him, Dr. Cannon would have worked ceaselessly for the Spanish outcasts in France, and he would have been sympathetic toward aiding a hospital to lighten their misery. He was always intimately involved with actual medicine and surgery, and for years the staff of the Peter Bent Brigham Hospital felt his close interest in their problems. Moreover, throughout World War I all his efforts while he was in France and England were directed toward solution of the clinical problems represented by surgical shock and hemorrhage. In World War II his interests continued in the same direction and were coupled with efforts to promote more intimate relations between productive scholars in different countries.

The memorial is finely appropriate to the man, and he in his turn would have been particularly happy that this just and merciful monument in his name is, at least in part, the gift of medical friends and colleagues. Many will remember how touched he was on the occasion of his twenty-fifth year as George Higginson Professor of Physiology, Harvard Medical School, that the funds for the celebration were subscribed in small amounts from several hundred former students and associates, and not in large contributions from a few. It is to be hoped that men and women in medicine will respond to this appeal by giving what they can. Good wishes mean much, but a good wish with a single dollar behind it can mean much more!

THE CARE OF THE PATIENT

We have become accustomed, in recent years, to think of the care of the patient from an economic and sociologic point of view — to fall in line with the theory, not now so startling as it once was, that the inhabitants of the earth should share more freely than was once the case in the fruits of their earth and in the benefits of human progress. From the tradition cherished at one time that the patient was a sort of bond servant of his practitioner, because of his own choice, we are gradually coming to entertain the idea that reasonably good medical care should be available, at least to most of us, at a price commensurate with our ability to pay, and that that cost, in fairness to the profession supply-

ing the service, should be spread over the whole population or certain segments of it.

Thus have come into being prepaid hospital-insurance plans, group practice as applied to industries, respectable coalitions of physicians to furnish medical service at a reasonable cost, as exemplified by the Blue Shield of the Massachusetts Medical Society, and, finally, impending federal control of certain types or parts of practice. This does not necessarily spell the doom of all private practice as we have known it, with its inadequacies and its inequalities both as to cost and as to quality, but it does mean that a social revolution is on the high road, and we might as well ride with it.

Many of these things will come to pass well or ill, wisely or unwisely, according to the will of the people and the ability of their representatives to plan, and since we cannot block them we had best try and direct them. What concerns us even more closely, because it is our medical skill that provides it, is the caliber of care that our fellow men receive from us. This we must not lose sight of when we are arguing over costs because we, and not the patient, know best the quality of our goods.

It is, of course, a truism to say that medical knowledge and the treatment and prevention of disease, which are the aims of medical knowledge, are making rapid advances. They have been making rapid advances since the authority of Galen was thrown off. What is important to recognize is that the art of medicine, valuable as it is, is becoming more and more simply an adjunct of the science. More and more the study and the treatment of the sick are being taken away from the home and the office and brought into the hospital and its contiguous laboratory.

Less and less is the practitioner — and this is no reflection on him — able alone to carry out the studies and institute the treatments that his patients may require. Hospital facilities must be available to him, but whether or not he is on the staff, those facilities are usually inadequate unless they include trained professional personnel — in the operating rooms, in the x-ray department, in the laboratory and on the ward.

Much of the best medical care now depends on teamwork, — this is the real revolution in medicine, — and this often implies the best hospital care in every sense of the word. One of the crying needs of medical practice today, so far as the technical care of the patient is concerned, is not simply to have a hospital to which the practitioner can take his patient and there care for him but rather to have a hospital to which he can take him and, if necessary, leave him to the care of those qualified in the details of modern medical procedures.

MASSACHUSETTS MEDICAL SOCIETY
POSTWAR LOAN FUND

The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:

George L. Schadt, *Chairman*
Postwar Loan Fund
8 Fenway
Boston 15, Massachusetts

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ELLIS — Edward K. Ellis, M.D., of Needham, died June 7. He was in his sixty-seventh year.

Dr. Ellis received his degree from Tufts College Medical School in 1902. He was a member of the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow survives.

OVERLANDER — J. Eliot Overlander, M.D., of Springfield, died May 26. He was in his sixty-sixth year.

Dr. Overlander received his degree from Harvard Medical School in 1909. He was formerly senior medical officer of the Springfield Hospital. He was a fellow of the American Medical Association.

His widow survives.

QUEST — James F. Quest, M.D., of Boston, died May 27. He was in his sixty-eighth year.

Dr. Quest received his degree from the University of Vermont College of Medicine in 1906. He was a fellow of the American Medical Association.

TREANOR — John P. Treanor, M.D., of Dorchester, died May 4. He was in his eighty-second year.

Dr. Treanor received his degree from Harvard Medical School in 1895. He was a member of the New England Pediatric Society and a fellow of the American Medical Association.

His widow survives.

MISCELLANY

DR. WALTER B. CANNON MEMORIAL HOSPITAL FUND

A memorial to Dr. Walter B. Cannon, late George Higginson Professor of Physiology at Harvard Medical School, is to be established in Toulouse, France. A hospital there, organized and staffed by Spanish refugees in France to serve their fellow refugees, is to be expanded and operated under its new name, the Dr. Walter B. Cannon Memorial Hospital.

Dr. Cannon, who was president of the American Association for the Advancement of Science in 1939, actively aided the Spanish Republicans from the start of the Civil War in 1936 to the end of his life. He became chairman of the Medical Bureau to Aid Spanish Democracy in 1937 and at his death was honorary co-chairman, Boston Chapter, Joint Anti-Fascist Refugee Committee. Through the Unitarian Service Committee, the Joint Anti-Fascist Refugee Committee has been helping 150,000 Spanish refugees remaining in France after three years of war and seven years of destitution and suffering. Ineligible for aid from the Red Cross, UNRRA or the French Government, these people without a country are as acutely in need of medical care as almost anyone in the world. They depend entirely on American charity.

About one hundred and fifty prominent Boston citizens have just started a drive for $75,000 to buy some of the necessary equipment for the hospital in Toulouse and to safeguard its continued operation. All funds are managed and spent in France by the Unitarian Service Committee. After Spain returns to democracy, the memorial to Dr. Cannon will be perpetuated there.

Co-chairmen of the drive are Dr. George R. Minot, professor of medicine, Harvard Medical School, Dr. Frederick May Eliot, president, American Unitarian Association, Ralph Barton Perry, professor of philosophy, Harvard University, and Paul T. Smith, attorney. Among the medical sponsors are Drs. Donald G. Anderson, Joseph C. Aub, Herrman L. Blumgart, Arlie V. Bock, Ethan Allan Brown, Allan M. Butler, William B. Castle, David Cheever, Stanley Cobb, Edwin J. Cohn, Hilbert F. Day, Robert L. DeNormandie, Cecil K. Drinker, John T. Edsall, Laurence B. Ellis, James M. Faulkner, Jacob Fine, Alexander Forbes, Channing Frothingham, James L. Gamble, Bernard I. Goldberg, Charles A. Janeway, Chester S. Keefer, Mary R. Lakeman, Eugene M. Landis, Samuel A. Levine, Moses H. Lurie, Helen I. D. McGillicuddy, J. H. Means, Leroy M. S. Miner, Dwight O'Hara, Marian C. Putnam, David Rapport, George C. Shattuck, Richard M. Smith, Paul D. White, George B. Wislocki and S. Burt Wolbach.

Headquarters of the Dr. Walter B. Cannon Memorial Hospital Fund are at 14 Beacon Street, Boston.

CORRESPONDENCE

FIRST USE OF X-RAYS IN BOSTON

To the Editor: The letter in the May 16 issue of the *Journal* on the first use of x-rays in Boston reminded me of an incident. As a student I sat in the staff chairs of the old amphitheater at the Massachusetts General Hospital waiting for Dr. Warren's lecture and reading the *Boston Post*, in which there was a short item mentioning that a Doctor Roentgen, of Vienna, had discovered a method of photographing the bones through the flesh. I circled it with a blue pencil and passed it to Dr. Warren when he came in. He read it and smiled, remarking, "That is a good newspaper story, isn't it, young man?" Before many months Dr. Warren was having his own cases x-rayed. I never got a chance to remind him of his remark.

Walter Dodd, who was the Massachusetts General Hospital pharmacist and who was interested in photography, took many pictures of pathological specimens. Being a snapshot amateur, I was interested in his work. In fear and trembling I got a picture of the dissecting room in the Boylston Street Medical School, and was caught by good old Tom Bonney, but gave him a print to placate him. Fond memories.

PHILIP C. MEANS, M.D.

Merrimac, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Periodontal Diseases and Soft Tissue Lesions of the Oral Cavity: Diagnosis and treatment. By Arthur H. Merritt, D.D.S., Sc.D. Third edition. 8°, cloth, 256 pp., with 53 illustrations. New York: Macmillan Company, 1945. $3.50.

The previous editions of this monograph contained only the text on periodontal diseases. In this third edition a second part, comprising six chapters on soft-tissue lesions of the mouth, has been added. The author's approach is clinical, and the original text has been revised and brought up to date.

A Textbook of Ophthalmology. By Sanford R. Gifford, M.D. 12°, cloth, 457 pp., with 215 illustrations, 4 charts and 13 plates. Philadelphia: W. B. Saunders Company, 1945. $4.00.

Dr. Gifford before his death completed the revision of the third edition of his small textbook first published in 1938. The text has been brought up to date, and new material has been added on ptosis, contact glasses, cyclodiathermy and keratoconjunctivitis. New illustrations in black and white have been incorporated in the text. Also twelve full-page color plates are used to delineate common diseased conditions of the eyes. The objective of the author, formerly professor at Northwestern University, was to compress into a small volume for medical students and general practitioners the essentials of modern ophthalmology. The need for three editions of his book speaks well for the attainment of his purpose.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 27

FRIDAY, JUNE 28
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

TUESDAY, JULY 2
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JULY 3
*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MARCH 15–SEPTEMBER 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

JUNE 20–22. American Association for the Study of Goiter. Page 312, issue of February 28.

JUNE 29. American College of Chest Physicians. Page 544, issue of April 18.

JULY 3. Harvard Medical Alumni Association. Page 808, issue of June 13.

SEPTEMBER 4–7 American Congress of Physical Medicine. Page 616, issue of May 2.

OCTOBER 6–12. Interamerican Congress of Cardiology. Page xix, issue of June 6.

OCTOBER 7–18. New York Academy of Medicine. Page 544, issue of April 18.

DISTRICT MEDICAL SOCIETY

PLYMOUTH

OCTOBER. Jordan Hospital, Plymouth.
NOVEMBER. Plymouth County Hospital, South Hanson.
JANUARY. Brockton Hospital, Brockton.
FEBRUARY. Moore Hospital, Brockton.
MARCH. Goddard Hospital, Brockton.
APRIL. State Farm, Bridgewater.
MAY. Lakeville Sanatorium, Lakeville.